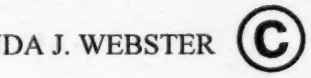
UNIVERSITY OF ALBERTA

TREATMENT OF ERECTILE DYSFUNCTION IN MALES WITH MODERATE HEART FAILURE: IMPACT ON DEPRESSIVE SYMPTOMS

BY

LINDA J. WEBSTER 

A THESIS SUBMITTED TO THE

FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF NURSING

FACULTY OF NURSING

EDMONTON, ALBERTA

FALL 2002

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-81348-7

Canada

University of Alberta

Library Release Form

Name of Author:	Linda J. Webster
Title of Thesis:	Treatment of Erectile Dysfunction in Males with Moderate Heart Failure: Impact on Depressive Symptoms
Degree:	Master of Nursing
Year this Degree Granted:	2002

Permission is hereby granted to the University of Alberta Library to reproduce single copies of this thesis and lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves all other publication and other rights in association with the copyright in the thesis, and except as herein before provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatever without the author's prior written permission.

Linda Webster

11530-9 Ave.
Edmonton, Alberta T6J 6T9

October 1, 2002

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify the they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled "Treatment of Erectile Dysfunction in Males with Moderate Heart Failure: Impact on Depressive Symptoms" submitted by Linda J. Webster in partial fulfillment of requirements for the degree of Master of Nursing.

Dr. T. Davis

Dr. S. Archer

Dr. C. Ross

Date Sept. 30/2002

Abstract

Although sildenafil is efficacious in treating ED, use in CHF is relatively contraindicated due to hypotensive concerns. It is proposed that ED, depression and CHF form a reinforcing triad. The purposes were to determine whether treatment of ED with sildenafil in males with moderate CHF would improve depressive symptoms, as well as validation of two depression indices. Thirty-five men were randomized into a 12-week, cross–over trial, comparing sildenafil to placebo. The International Index of Erectile Function (IIEF), Beck Depression Index (BDI), and Center of Epidemiologic Studies–Depression (CES-D) scales were completed at baseline, and after 4 weeks of sildenafil/placebo. ANOVA and Fisher's PSLD were used. Sildenafil was effective in improving the IIEF score ($p<0.0001$). This was associated with decrease in BDI ($p<0.005$) and CES-D ($p<0.003$) scores, which showed 83% concordance. Effective treatment of ED is associated with improvement of depression in patients with moderate CHF. The BDI and CES-D indicated concordance.

ACKNOWLEDGEMENTS

With the completion of this thesis, another phase of my life concludes. The journey of this thesis has probed my strengths and weaknesses, only to result, I hope, in helping me to learn more about myself and helping me to become a better person.

Several individuals have made the completion of this thesis possible and deserve special mention and gratitude:

To my brothers and "sisters" (Doug, Jane, Ken & Kathy), for offering encouragement and support along the way.

To Colleen Brayman & Norma Hogg, who offered friendship, laughter, and strong shoulders to lean on.

To Dr. Stephen Archer, my supervisor, who also stood by me when things got difficult and offered unwaivering support.

Special thanks to Dr. Terry Davis, my supervisor. Your patience and thoughtful repartee made the completion of this thesis a reality. Thanks also to Dr. Carolyn Ross for being a part of the process.

DEDICATION

This thesis is dedicated to my parents, Pat and Frank Webster, who, without their love and support, I could not have completed this endeavour.

Also, to my son Austin, who showed patience and understanding far beyond his eleven years.

TABLE OF CONTENTS

Abstract
Acknowledgements
Table of Contents
List of Tables
List of Figures

		Page
Chapter 1	INTRODUCTION	1
	Purpose of Study II	3
Chapter 2	LITERATURE REVIEW	5
	Goldstein's Model: Congestive Heart Failure, Erectile Dysfunction and Depression	5
	Congestive Heart Failure	5
	Erectile Dysfunction	6
	Depressed mood, Depressive Symptoms and Clinical Depression	8
	Depressed Mood	8
	Depressive Symptoms	9
	Clinical Depression	9
	Dysthymic Disorder	11
	Comorbidity among the Conditions	11
	Congestive Heart Failure and Depression	13
	Congestive Heart Failure and Erectile Dysfunction	15
	Depression and Erectile Dysfunction	16
	Congestive Heart Failure, Erectile Dysfunction and Depression	18
	Summary	19
Chapter 3	METHODOLOGY	21
	Trial Design	21
	Subject Selection and Recruitment	21
	Recruitment	21
	Selection	23
	Study 1: Safety and Efficacy Protocol	24
	Safety Protocol	24
	Efficacy of Erectile Function Protocol	27
	Study 2 Assessment of Depression	27
	BDI	29
	CES-D	30
	Ethical Considerations	31
	Statistical Analysis	32
	Sample Size Calculation	32
	Data Analysis	33

Chapter 4	RESULTS	34
	Participant characteristics	34
	The Relationship of Depressive Symptoms and Erectile Dysfunction in Males with Congestive Heart Failure Before and After Treatment	37
	Summary of IIEF, BDI and CES-D Scores	37
	Efficacy of Erectile Function (IIEF) - Results	39
	Treatment of Erectile Dysfunction and BDI scores – Results	42
	Treatment of Erectile Dysfunction and CES-D scores – Results	42
	Severity of Depressive Symptoms	45
	Comparison of the BDI and the CES-D as Screening Tools for Depression in Males with Moderate Heart Failure	47
	Concordance between the BDI and CES-D	47
	Referral for Diagnostic Assessment	48
	Effect of Somatic Symptoms on Depressive Index Scores	48
	Treatment of Erectile Dysfunction and BDI Scores (Somatic Items Omitted) - Results	50
	Treatment of Erectile Dysfunction and CES-D Scores (Somatic Items Omitted) - Results	55
Chapter 5	SUMMARY AND DISCUSSION	56
	The Relationship of Depressive Symptoms and Erectile Dysfunction in Males with Congestive Heart Failure Before And After Treatment	56
	Efficacy if Erectile Function	56
	Treatment of Erectile Dysfunction and Depressive Index Scores	58
	Comparison of the BDI and CES-D as Screening Tools for Depression in Males with Moderate Heart Failure	60
	Limitations of the Study	63
	Assessment of Erectile Dysfunction	64
	BDI Cutoff Score	64
	Implications for Clinical Practice	64
	Future Research	65
	Conclusion	66
REFERENCES		67
APPENDIXES		
A	Permission – Elsevier Science	77
A	Erectile Physiology and Treatment of Erectile Dysfunction	78
	Erectile Physiology	78
B	The Treatment of Erectile Dysfunction	80
	Sildenafil	80

	Pharmacology of Sildenafil	82
C	Sildenafil and Congestive Heart Failure	83
	Safety of Intercourse and congestive heart failure	85
D	Letter of Invitation	86
E	International Index of Erectile Function	87
F	Center for Epidemiologic Studies – Depression Scale	90
G	Ethics Approval	91
H	Ethics Approval – Addendum 1	92
I	Addendum 1	93
J	Sample size Calculations	97
K	Permission for use of Figure (Michelakis)	98

LIST OF TABLES

Table		Page
1	Protocol Procedures for Study I and Study II	22
2	Participant Clinical Characteristics in Study I and Study II	35
3	Statistical Analysis of Baseline Characteristics between the Treatment Groups (sildenafil first and placebo first)	36
4	Participants Total Scores (IIEF, BDI, CES-D) at Baseline, Week 4 and Week 10 – Sildenafil First	38
5	Index Scores at Baseline, Week 4, and Week 10 [Range (Mean + SEM)] - Sildenafil first	37
6	Total Scores (IIEF, BDI, CES-D) at Baseline, Week 4 and Week to - Placebo First	40
7	Index Scores at Baseline, Week 4, and Week 10 [Range (Mean + SEM)] - Placebo first	39
8	Severity of Depressive Symptoms: Total BDI Scores [Number (Percentage of total sample)] by Treatment Group (Sildenafil first and Placebo first) at Baseline, Week 4, and Week 10	46
9	Summary of Participant's Positive Screening Scores (total) by Reporting Period, Treatment and Depressive Index Scores	49
10	Participants Scores (total IIEF, total BDI – somatic scores, total CES-D somatic scores) at Baseline, Week 4 and Week 10 – Sildenafil first	51
11	Participants Scores (total IIEF, total BDI – somatic scores, total CES-D somatic scores) at Baseline, Week 4 and Week 10 – Placebo first	52
12	Sample Size Table for Means of 12-20 accepting a Standard Deviation of 10	98

LIST OF FIGURES

Figure		Page
1	Goldstein's mutually reinforcing triad	2
2	DSM-IV criteria for major depressive episode	10
3	DSM-IV criteria for dysthymic disorder	12
4	Study I: safety protocol algorithm	26
5	International index of erectile function: questions of the erectile domain	28
6	Total scores of IIEF (efficacy of erectile function domain) at baseline, week 4 and week 10	41
7	Total scores of BDI at baseline, week 4, and week 10	43
8	Total scores of CES-D at baseline, week 4, and week 10	44
9	BDI scores (somatic questions omitted) at baseline, week 4 and week 10	53
10	CES-D scores (somatic questions omitted) at baseline, week 4 and week 10	54
11	The mechanism of erection and the role of nitric oxide	79
12	The intracellular activities within a single smooth muscle cell and the effect of sildenafil on erection	81

Treatment of Erectile Dysfunction in Males with Moderate Heart Failure: Impact on Depressive Symptoms

CHAPTER 1

Introduction

Cardiovascular disease, depression, and erectile dysfunction were once thought to be three separate conditions and were treated as such. Today, however, these conditions are presumed to have significant comorbid associations with reciprocal causality (Goldstein, 2000). To explicate this relationship, Goldstein (2000) developed a model which he entitled the "Mutually Reinforcing Triad" (see Figure 1). In Goldstein's model the conditions of cardiovascular disease, depression, and erectile dysfunction are presented as forming the sides of a triangle. If an individual has all three conditions named in the triad, then changes in one affects the others. For example, with the improvement of symptoms of cardiovascular disease, improvement of erectile dysfunction and symptoms of depression would be expected.

In Goldstein's model, cardiovascular disease is addressed in the generic sense. In order to test the validity of Goldstein's model as it would translate to the cardiovascular condition of congestive heart failure, two concurrent studies involving the same group of male patients with moderate congestive heart failure [New York Heart Association (NYHA) Class II – III], were conducted. Study I (conducted by Linda Webster, RN, BScN, Evangelos Michelakis, MD, and Stephen Archer, MD) investigated the safety and efficacy of sildenafil in the treatment of erectile dysfunction in males with moderate congestive heart failure (NYHA Class I – II). The safety of sildenafil in the study

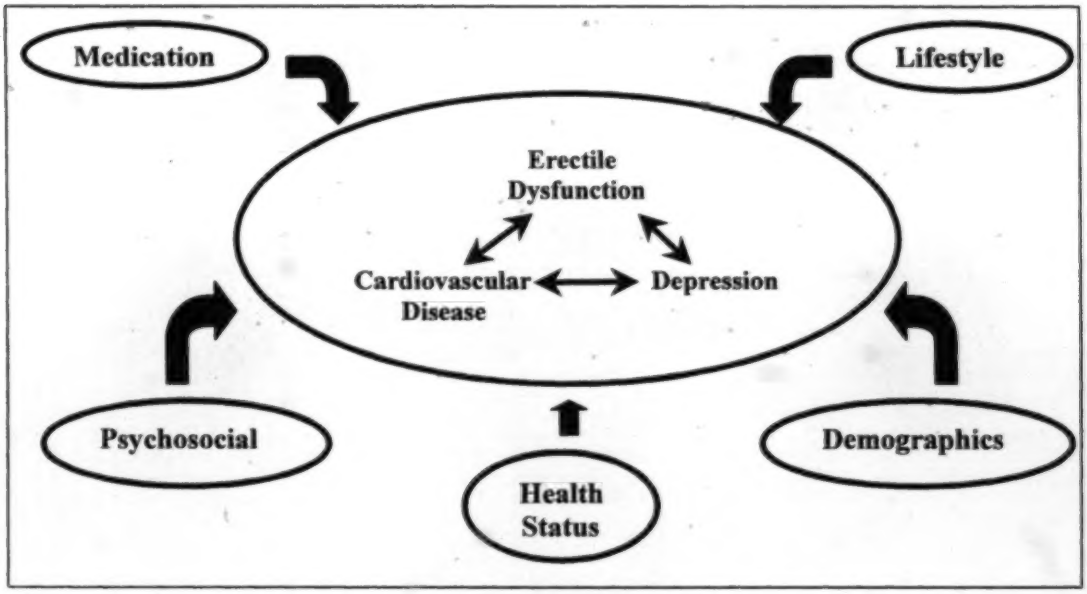


Figure 1. Goldstein's mutually reinforcing triad (Goldstein, 2000)[1].

[1]From "The Mutually Reinforcing Triad of Depressive Symptoms, Cardiovascular Disease, and Erectile Dysfunction" by I. Goldstein, 2000, *American Journal of Cardiology, 86,* p. 45F. Copyright 2000 by the American Journal of Cardiology. Adapted with permission of the journal (see Appendix A).

participants was addressed by ensuring adequate fitness for sexual activity, absence of myocardial ischemia, and adequate ambulatory blood pressure for 4 hours following the ingestion of sildenafil (50 mg) in the clinic setting. Efficacy was addressed utilizing the International Index of Erectile Function (IIEF), the Minnesota Living with Heart Failure Questionnaire (LIhFE), and participant diaries. Study II (conducted by Linda Webster, RN, BScN), which comprised this thesis, investigated the relationship between depressive symptoms and erectile dysfunction in males with congestive heart failure before and after treatment with sildenafil. This was accomplished by utilizing the Beck Depression Index (BDI) and the Center for Epidemiology Studies – Depression Scale (CES-D) to measure depressive symptoms and their severity. Both studies were funded with a grant from the University of Alberta Hospitals Foundation.

It is important to note that prior to the clinical trial involving these two studies, the treatment of erectile dysfunction in males with moderate congestive heart failure had not previously been investigated. Indeed, treatment with sildenafil in this group was believed to be "relatively contraindicated" (NIH Consensus Conference, 1993). However, since it was known that depression (Freedland et al., 1991) and erectile dysfunction (Jaarsma, Dracup, Walden, & Stevenson, 1996; Plaud et al., 1996) affects these patients to a larger degree than their healthy counterparts, and since both conditions significantly influence the well-being of congestive heart failure patients, determination of effective treatment options was deemed important.

Purpose of Study II

The twofold purpose of this study was to investigate the relationship between depressive symptoms and erectile dysfunction in males with moderate congestive heart

failure (NYHA Class II-III) before and after treatment with sildenafil, and to compare the BDI and CES-D as screening tools for clinical depression in males with moderate congestive heart failure (NYHA Class II-III).

CHAPTER 2

Literature Review

The prevalence and incidence rates of congestive heart failure, erectile dysfunction, and depression and their etiology were examined separately, as well as their co-occurrence using Pub med (January 1975 – present). In addition, the measurement strategies (tools) used by researchers to determine erectile dysfunction used in past research were considered. The publication search was then narrowed to the years of 1998-present (2002), as this would coincide with the market release of sildenafil and the period in which this thesis was completed.

Abstracts from retrieved publications were reviewed for suitability of content. The full publication was obtained from library periodical stacks when content was believed to contribute to the purpose of this thesis.

Goldstein's Model: Congestive Heart Failure, Erectile Dysfunction, and Depression

Congestive Heart Failure

The textbook definition of congestive heart failure is the "pathophysiologic state in which the heart is unable to pump blood at a rate commensurate with the requirements of metabolizing tissues or can do so only from elevated filling pressures" (Cheng, 1999, p. 433). Several definitions based on severity of symptoms and functional ability have been proposed, but the aforementioned definition embodies the meaning of the disease.

Congestive heart failure affects 0.1% - 0.5% of the world population (Kannel & Belanger, 1991). Extrapolation from United States data (Yusuf, Thom, & Abbott, 1989) suggests that approximately 250,000 Canadians (approximately 150,000 males) are estimated to have congestive heart failure (Teo et al., 1992).

The literature reveals there is a marked increase in incidence of congestive heart failure with advancing age from 0.5% per year at age 45 to almost 1% year over 75 years of age (Cowie et al., 1997; Massie & Shah, 1997; Senni et al., 1999). This trend remained relatively unchanged in a study conducted by Senni et al.(1999) from 1981 – 1991. It is believed that the incidence of congestive heart failure will increase due to the aging population as well as decreased morbidity from myocardial infarction (Dominguez, Parrinello, Amato, & Licata, 1999).

The annual incidence of congestive heart failure as it relates to gender was addressed in the Framingham Heart Study[2]. This study showed that women consistently had a lower incidence of congestive heart failure but this gap narrowed in later decades of life (Kannel & Belanger, 1991).

Erectile Dysfunction

The problem of erectile dysfunction can be discussed once the process of normal erection is understood. An overview of this process can be found in Appendix B. Erectile dysfunction is defined as "the complete OR partial inability to maintain an erection and functional inability to achieve satisfactory penetration necessary for completion of sexual intercourse" (NIH Consensus Conference, 1993, p. 83). The National Institute of Health (NIH) Consensus Conference (1993) renamed and redefined

[2]The Framingham Heart Study (FHS) was started in 1948 as a prospective study of heart disease in men and women. 5209 subjects were followed through biennial contact. In 1971 examinations were begun on children of the FHS cohort. This study was undertaken to expand upon knowledge of cardiovascular disease, particularly in the area of familial clustering of the disease and its risk factors (Kannel, Feinleib, McNamara, Garrison, & Castelli, 1979).

this form of sexual dysfunction[3] as impotence implied an absolute inability to attain erections. Functional inability included erections that were not sustainable or which occurred inconsistently (NIH Consensus Conference, 1993). The most common causes of erectile dysfunction are vascular, neurologic, and iatrogenic whether pharmacologic (Langtry & Markham, 1999) or surgical (Mertens, Merckx, Derluyn, & van den Brande, 1994). A psychological component of erectile dysfunction exists in some individuals (Burchardt et al., 2001).

A group of researchers in the Massachusetts Male Aging Study (MMAS)[4] (Johannes et al., 2000; Manecke & Mulhall, 1999; Melman & Gingell, 1999) found that the lifetime prevalence of any form of erectile dysfunction is 39% of 40 year olds and 67% of 70-year-old men. Complete impotence (inability to achieve an erection) was reportedly experienced by 5% of men aged 40 and 15% of men aged 70 years (Wagner & Saenz de Tejada, 1998).

[3]Sexual dysfunction is the "disturbance in sexual desire and the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty" (Seidman & Roose, 2001). The distinct areas that are encompassed in the umbrella term of sexual dysfunction are (Seidman & Roose, 2001):

1. Sexual desire disorders (hypoactive sexual desire, sexual aversion).
2. Sexual arousal disorders (female sexual arousal disorder, **male erectile disorder**).
3. Orgasmic disorders (female/male orgasmic disorder, premature ejaculation).
4. Sexual pain disorders (dyspareunia, vaginismus).
5. Sexual dysfunction due to general medical conditions.
6. Substance-induced sexual dysfunction.
7. Sexual dysfunction not otherwise specified.

The classifications are clearly not mutually exclusive. Sexual dysfunction is further classified with regards to onset (lifelong or acquired), context (generalized or situational) and etiological (psychological or combined) factors (Seidman & Roose, 2001).

[4]The MMAS began in 1987 and is a community-based survey of health and aging in men. It consists of a random sample cohort and is considered a landmark research effort in the fields of aging, urology, and endocrinology (McKinlay, 1989).

The MMAS further documented that the incidence of erectile dysfunction is likewise increased with advancing age (Benet & Melman, 1995; Langtry & Markham, 1999). In a longitudinal study, these same researchers found that the incidence of erectile dysfunction increased with other risk factors such as lower education (less than a high school diploma), diabetes, heart disease and hypertension (Johannes et al., 2000). It is important to note that erectile function was assessed using the IIEF, which was developed specifically for the purpose of the MMAS. In previous studies, erectile function was assessed using subjective self-report diaries and/or nocturnal penile tumescence measurement procedures. The self-report diaries were criticized for the possibility of underestimation of sexual activity or confabulation of extensive sexual activity. Penile tumescence offered moderate test-retest reliability as the participants applied the devices independently and the method by which this is done may have been inconsistent (Harding & Golombok, 2002).

Several options exist for the treatment of erectile dysfunction. Sildenafil treatment utilized for the purpose of these studies is described in Appendix C.

Depressed Mood, Depressive Symptoms, and Clinical Depression

Before presenting the incidence and prevalence, findings for clinical depression, depressed mood, depressive symptoms and clinical depression will be differentiated. These terms are often used incorrectly and interchangeably in practice and in the literature.

Depressed mood. Depressed mood is defined as "a tendency to sadness" (U.S. Department of Health and Human Services, 1993, p. 37). Often people describe this depressed "feeling" state by using terms such as "feeling down", "feeling blue", or

"feeling sad" (Gutierrez, 1997). If the feeling state persists, then the person is said to have depressed mood. Prevalence and incidence data is not available for depressed mood in any given population.

Depressive symptoms. Depressive symptoms tend to occur if depressed mood is prolonged. Depressive symptoms may include disturbances in cognition (e.g., difficulty in concentrating, and inability to make decisions), disturbances in behavior (e.g., psychomotor retardation and self-isolation), and disturbances in somatic functioning (e.g., fatigue, and loss of libido) (U.S. Department of Health and Human Services, 1993). No incidence or prevalence data are available for depressive symptoms within a defined population.

Clinical depression. According to the DSM-IV[5], clinical depression involves a depressed mood and a set of depressive symptoms. The most recent definitions may be found in the DSM-IV-TR criteria published in 2000 (see Figure 2).

A person is diagnosed as having Major Depressive Disorder if they experience one or more Major Depressive Episodes over their lifetime. Depressive symptoms, and to a lesser extent, Major Depressive Episodes/Major Depressive Disorders, are frequently observed in medical practice (Lecrubier, 2001); however, causation is often difficult to determine (Peveler, Carson, & Rodin, 2002).

The incidence of clinical depression in a given population was not cited in any retrieved literature. The prevalence of lifetime risk for the development of a Major Depressive disorder in random community samples has varied from 10% - 25% for

[5] The American Psychiatric Association developed the definition of Major Depressive Episode in 1952 in the Diagnostic and Statistical Manual of Mental Disorders – first edition (DSM – I) (American Psychiatric Association, 2000).

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least on the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% body weight in a month), or decrease or increase in appetite nearly every day.
4. insomnia or hypersomnia nearly every day.
5. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. fatigue or loss of energy nearly every day.
7. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan for committing suicide.

Figure 2. DSM-IV criteria for major depressive episode (American Psychiatric Association, 2000).[6]

[6]From "Major Depressive Episode" by The American Psychiatric Association, 2000, *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision – DSM-IV-TR,* p.356. Copyright 2000 by the American Psychiatric Association. Public domain.

women and 5% – 12% for men. These percentages were found to be unrelated to ethnicity, education, income, or marital status (American Psychiatric Association, 2001).

Dysthymic disorder. Dysthymic disorder has been defined as a chronically depressed mood and depressive symptoms that occur for most of the day, more days than not, for at least two years (American Psychiatric Association, 2001). The diagnostic criteria for dysthymic disorders can be reviewed in Figure 3.

No data was provided for the incidence for dysthymic disorder. The prevalence of dysthymic disorder is approximately 6%. It may occur simultaneously with a Major Depressive Episode or Major Depressive Disorder which may predispose the individual to a "double depression" (American Psychiatric Association, 2001).

Comorbidity Among the Conditions

The concept of comorbid conditions, in which two or more conditions concurrently exist within the same individual, is central to this thesis. Comorbid conditions are often designated as primary or secondary based on the onset of the first condition (primary) (Feinstein, 1970). This distinction was classically applied to psychiatric conditions when they occurred with physical illness (Feinstein, 1970). Two concerns arise with regards to the distinction primary and secondary conditions and the direction of causality:

1. Overlapping symptoms for which the underlying condition may be confound the conditions as primary or secondary. For example, the symptom of fatigue may occur with either depression or congestive heart failure thereby could not be clearly attributed to either condition.

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years.

B. Presence, while depressed, of two or more of the following:
   (1) poor appetite or overeating
   (2) insomnia or hypersomnia
   (3) low energy or fatigue
   (4) low self-esteem
   (5) poor concentration or difficulty making decisions
   (6) feelings of hopelessness

C. During the 2-year period (1 year for children and adolescents) of the disturbance, the person has never been without the symptoms in Criteria A and B for more than 2 months at a time.

D. No Major Depressive Episode has been present during the first 2 years of the disturbance (1 year for children and adolescents); i.e., the disturbance is not better accounted for by chronic Major Depressive Disorder, or Major Depressive Disorder, in Partial Remission.

E. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder.

F. The disturbance does not occur exclusively during the course of a chronic Psychotic Disorder, such as Schizophrenia or Delusional Disorder.

G. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Figure 3. DSM-IV criteria for dysthymic disorder (American Psychiatric Association, 2001)[7].

[7]From "Major Depressive Episode" by The American Psychiatric Association, 2000, *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision – DSM-IV-TR,* p.356. Copyright 2000 by the American Psychiatric Association. Public domain.

2. Directional causality is not often as clear as one might assume. One condition, though often related to the other, may exist in parallel without being directly caused by the first.

Congestive Heart Failure and Depression

Individuals with chronic medical conditions are at increased risk of developing a Major Depressive Disorder (20% - 25%) (American Psychiatric Association, 2001). Depressive symptoms and heart failure have been found to frequently co-exist. Several studies have investigated those diagnosed with congestive heart failure and the presence / severity of depressive symptoms (Freedland et al., 1991; Friedman & Griffin, 2001; Gutierrez & Davis, 1999; Jiang et al., 2001).

Freedland et al. (1991) studied MDE in 60 patients over the age of 70 (males and females) admitted to hospital with congestive heart failure. Medical staff using an interview tool based on DSM-III criteria determined the presence of depression. This study found that 17% met the criteria for an MDE regardless of age or sex. Follow-up phone calls were conducted at three months and 1 year post enrollment. The study team found greater mortality rates in those congestive heart failure patients that had experienced MDE (50%) when compared with those that had not (29%) (Freedland et al., 1991). This difference failed to achieve significance, but a strong trend was noted.

Gutierrez and Davis (1999) assessed the prevalence of depression in a sample of heart failure patients (males and females) with varying severity of disease. This was accomplished using the BDI and structured interviews using DSM-IV criteria. A greater percentage of the female sample was found to have depressive symptoms (20%) when compared to their male counterparts (10%) however, severity of symptoms was found to

be a predictor for occurrence of depression only in the male participants. This finding was absent in the female participants.

Friedman and Griffen (2001) studied the relationship of levels of physical functioning and symptoms to depression in a heart failure population. The measurement tools utilized in this study were a 13-item symptom checklist, the Medical Outcomes Study Short Form Health Survey and the CES-D. In a sample of 170, they found a 30% prevalence of depression in patients admitted to hospital with congestive heart failure. This is significantly higher than the 11% previously shown in cohorts of males without congestive heart failure (Andresen, Malmgren, Carter, & Patrick, 1994). The severity of depression and/or depressive symptoms was a strong predictor for the endpoints of declining functional capacity (actual and perceived). They also reported that physical symptoms increased with the number and severity of reported symptoms of depression.

Jiang et al. (2001) found a high correlation between depression and increased risk of mortality and rehospitalization in a population with congestive heart failure (Jiang et al., 2001). They administered the BDI and a Mental Health Diagnostic Interview to 374 patients admitted for congestive heart failure. The participants who scored > 10 on the BDI and had a positive screening interview for depression had significantly greater incidence of death and rehospitalization (3 months and 1 year). This finding was independent of age, NYHA class, baseline ejection fraction, and ischemic etiology of congestive heart failure when compared to their cohorts that did not screen positive for depressive symptoms or depression.

To establish if the converse relationship could exist, in other words if depression could cause congestive heart failure, Williams et al. (2002) followed 188 individuals,

which had scores indicative of depression on the CES-D for 14 years. Depression was not found to be a predictor for heart failure in the elderly male population, but interestingly was predictive of the development of congestive heart failure in elderly women.

Congestive Heart Failure and Erectile Dysfunction

Males with congestive heart failure remain interested in sexual activity (Jaarsma et al., 1996). The very nature of the disease would suggest that congestive heart failure contributes to the likelihood of erectile dysfunction (Cleland & Wang, 1999; DeBusk et al., 2000; Friedman, 2000). Patients diagnosed with congestive heart failure experience erectile dysfunction more frequently than the normal population for two primary reasons:

1. Vascular disease: Virtually all congestive heart failure patients have overt vascular disease and/or endothelial dysfunction. (Jaarsma, Dracup, Walden, and Stevenson, 1996).
2. Polypharmacy: Medications used in the treatment of congestive heart failure (e.g., diuretics, beta-blockers, digitalis) may precipitate or worsen erectile dysfunction (Buffum, 1986).

Treatment of erectile dysfunction in males with congestive heart failure and the safety concerns associated with sildenafil treatment in this population is discussed in Appendix D.

Jaarsma et al. (1996) conducted a descriptive study that discussed sexual function in males and females with advanced congestive heart failure (NYHA Class III & IV). The authors administered The Psychological Adjustment to Illness Scale that showed that libido and sexual performance worsened as congestive heart failure progressed. The

authors did not establish correlation between subsequent improvement of congestive heart failure and sexual performance. This was a descriptive study as no directional causality was possible to determine. The clients' psychological state during symptomatic exacerbation or improvement was not addressed as contributing to overall sexual function.

There is no literature to support the opposite causality of erectile dysfunction causing congestive heart failure. Erectile dysfunction may exist in parallel to congestive heart failure and not be a result of congestive heart failure.

The MMAS documented that erectile dysfunction was found to be more prevalent in men with cardiovascular disease (60%) regardless of age (Benet & Melman, 1995). This was in agreement with later clinical investigations by Friedman (2000), and Drory, Kravetz, Florian, and Weingarten (1998) in which they determined that 50-75% of men after a myocardial infarction experience erectile dysfunction, although this estimate included very mild forms of erectile dysfunction. No prevalence is available in the literature specifically pertaining to males with congestive heart failure.

Depression and Erectile Dysfunction

Erectile dysfunction, and the emotional distress that frequently accompanies it, may precipitate depression in vulnerable men, likewise depression may cause erectile dysfunction, or both conditions may coexist and reinforce the other. Goldstein stated that when the comorbidities of erectile dysfunction and depression were present, severity of erectile dysfunction increased with advancing age while symptoms of depression did not become worse with advancing age (Goldstein, 2000). Several groups of researchers (Araujo, Durante, Feldman, Goldstein, McKinlay, 1998; Feldman, Goldstein,

Hatzichristou, Krane, & McKinlay, 1994; Roose & Seidman, 2000) found that erectile dysfunction and depressive symptoms usually existed as comorbid states, though primary and secondary distinction was difficult to determine.

Feldman et al. (1994), studied psychosocial correlates as they related to erectile dysfunction in the MMAS. Responses to sexual function questionnaires (1290 participants) indicated that severity of depression and degree of erectile dysfunction was directly correlated. For example, moderate degrees of erectile dysfunction on the IIEF, were often related to moderate degrees of depressive symptoms on the CES-D. Araujo et al., did a cross sectional analysis as part of the MMAS and found that the relationship between erectile dysfunction and depression was "robust and independent of important aging and para-aging confounders, such as demographic, anthropometric and lifestyle factors, health status, medication use, and hormones" (Araujo et al., 1998). Roose and Seidman (Roose & Seidman, 2000) supported these findings when their review of current literature suggested that the comorbid presence of erectile dysfunction and depression reinforced and exacerbated each within the individual.

A team of researchers worked stringently to determine directional causality of erectile dysfunction and depression. Their conclusions found that it was often difficult to determine the primary and secondary distinction of erectile dysfunction and depression when they exist concomitantly (Seidman, 2002; Seidman & Roose, 2000, 2001).

Muller and Benkert (2001) studied the role of treatment of erectile dysfunction and various depressive states. They studied 54 men with erectile dysfunction and without the presence of confounding disease. They found that self-reported symptoms of

depression reported by the CES-D showed significant improvement when their erectile dysfunction was successfully treated with sildenafil.

Shabsigh, Zakaria, Anastasiadis, & Seidman (2001) studied 100 men. One third of them had erectile dysfunction without any comorbid etiology, a second third had benign prostatic hypertrophy without the complication of erectile dysfunction, and a third group had both conditions. Following completion of the BDI with all three groups, they determined that there was a significant difference in the incidence of depression in males with erectile dysfunction (54%), compared to men without erectile dysfunction (26%), even after adjusting for age, marital status, or other comorbidities.

The MMAS studied men's incidence of erectile dysfunction and their reported levels of depression using the CES-D. These were males from a population with varying degrees of erectile dysfunction and co-morbidities. A strong positive association between erectile dysfunction and depressive symptoms was found. The odds ratio was 2.03 (95% confidence interval of 1.39 – 2.96). This concluded that men with erectile dysfunction experienced depressive symptoms to a great extent (Goldstein, 2000).

Congestive Heart Failure, Erectile Dysfunction, and Depression

There is no literature about the co-occurrence, prevalence or incidence of the three conditions existing together. This is the first documented study that will study this relationship in the context of Goldstein's mutually reinforcing triad.

Summary

In summary:

1. Congestive heart failure affects approximately 150,000 Canadian males with that number ever increasing due to reduced mortality rates following myocardial infarctions and increasing life expectancy.
2. Erectile dysfunction affects 39% of 40-year-old males increasing to 67% of 70 year olds. The effects of this condition are more pronounced in the presence of chronic vascular disease such as congestive heart failure.
3. Depressed mood, depressive symptoms, and clinical depression affect 5-12 % of males in the general population. Every person experiences, at the very minimum, periods of depressed mood in response to life events.
4. Congestive heart failure patients experience depressive symptoms and depression at significantly higher rates (17% - 30%) when compared to healthy cohorts (11%). Those with depressive symptoms/depression have higher mortality and rehospitalization rates independent of other components of their condition. Congestive heart failure has been shown to cause depression, but the reverse relationship was disproven in the male population.
5. Congestive heart failure and erectile dysfunction are known to coexist given the vascular impairment and polypharmacy. Males with generic cardiovascular disease have a prevalence of 60% of erectile dysfunction independent of other conditions. No statistical data exists specific to congestive heart failure. Congestive heart failure has been shown to cause

erectile dysfunction, but the reverse causal relationship has not been addressed in any study.

6. Depression and erectile dysfunction frequently co-exist as shown by a prevalence of 54% of males with erectile dysfunction indicating symptoms of depression when compared to 26% of their cohorts with no documented erectile dysfunction. Causality is bi-directional and studies designed to determine causality have failed to do so to date.

7. Goldstein (2000) suggested that the conditions of congestive heart failure, erectile dysfunction and depression are mutually reinforcing. No studies have validated this intrinsic relationship.

To date, no published studies have explored the manipulation of erectile dysfunction in order to explore refractory improvement in depressive symptoms within the male congestive heart failure population.

CHAPTER 3

Methodology

Trial Design

The design of Study I was a 12-week randomized, placebo-controlled, cross-over study in which the participants received sildenafil and placebo for 6 weeks each. Six pills of either sildenafil or placebo were given for each two-week period. Study II involved assessing depressive symptoms in study participants before and after each treatment. The assessment procedures that were utilized in Study I are outlined in Table 1 with the additional questionnaires utilized in Study II appearing in the shaded boxes.

The randomized, placebo-controlled, cross-over study design was chosen for the following reasons: (1) to enable all participants to potentially experience improved erectile function; (2) to allow each participant to serve as his own control, thereby allowing investigators to compare treatments within subjects rather than among subjects; (3) to permit assessment of psychological factors associated with erectile dysfunction, and (4) to retain the statistical power necessary to determine significant treatment effects, given the size of the clinic population the participants were recruited from [Myers-Grender & Johnson, 1994].

Subject Selection and Recruitment

Recruitment

Male patients being followed by the University of Alberta Heart Function Clinic formed the population for Study I and Study II. These patients were pre-screened to exclude those currently prescribed routine nitrates. The investigators sent a letter of

Table 1

Protocol Procedures for Study I and Study II

Assessment Strategy	Week of Protocol								
	-1	0	1	2	4	6	8	10	12
Stress test	X								
ECG	X								
Ambulatory BP	X								
IIEF		X			X			X	
LIhFE		X			X			X	
CES-D		X			X			X	
BDI		X			X			X	
Pill Count			X	X	X	X	X	X	X
Interview		X	X	X	X	X	X	X	X
Review diary			X	X	X	X	X	X	X
Side effects			X	X	X	X	X	X	X

Note. ECG = electrocardiogram, BP = blood pressure.

invitation (see Appendix E) to potential participants as a form of initial contact. The letter briefly described the study and offered the reader an opportunity to contact a member of the study group for details about enrollment if he experienced erectile dysfunction. A total of seventy-three letters were mailed and thirty-eight (52.05%) men responded.

Selection

The 38 patients who positively responded to the initial introductory letter by contacting a member of the study team were screened for further suitability for participation using the following inclusion and exclusion criteria:

Inclusion criteria were very liberal: NYHA Class II-III, and able to achieve a minimum of 5 METS without evidence of ischemia. The minimum MET requirement for study participation ensured that subjects had a level of general cardiovascular fitness necessary for sexual activity. Class IV patients were excluded because of their inability to exercise and to minimize the risk of negative hemodynamic effects. Class I patients were excluded because of their lower morbidity (Cheng, 1999), treatment profile (Teo et al., 1992), and decreased incidence of depressive symptoms when compared to their NYHA Class II & III cohorts (Majani et al., 1999; Vaccarino, Kasl, Abramson, & Krumholz, 2001). Moreover, Class I patients would not enable the investigators to address the purpose of the clinical trial to study the potential hemodynamic compromise and impact on depressive symptoms of the use of sildenafil in this population.

Exclusion criteria included: 1). NYHA Class I or IV, 2). Nitrate therapy, 3). Symptomatic hypotension or systolic BP < 80mmHg, 4). Positive stress test indicative of ongoing ischemia, 5). Significant aortic stenosis, 6). Recent history of drug and/or

alcohol abuse, 7). Inability to give informed consent. The exclusion criteria largely served to eliminate those persons to which sildenafil may have posed physiological risk. Sildenafil possesses minor vasodilatory properties that may enhance the effect of hypotension caused by concurrent prescribed heart failure regimes. The participants had to maintain a blood pressure greater than 80mmHg with no orthostatic symptoms post-sildenafil ingestion in order to continue in the study. As an additional safety measure, since sildenafil had not been given in congestive heart failure, the effect of sildenafil on ambulatory blood pressure was measured for 4 hours following a test dose of sildenafil (50mg). The additional exclusion criteria of psychotropic therapy (anxiolytics or antidepressants) was added to exclude those persons that were previously diagnosed with depressive/psychiatric disorders that would have confounded Study II.

Three patients who responded to the letter of invitation were excluded for nitrate use that had not been documented on their Heart Function Clinic records. A total of thirty-five male patients were enrolled in the Study I and Study II.

Study I: Safety and Efficacy Protocol

Safety Protocol

The participants demonstrated minimal functional capacity during a modified Bruce protocol in which they were to achieve at least 5 METS without evidence of ischemia. If the presence of ischemia [electrocardiographic (ECG) changes $\geq$ 1 mm flat ST segment depression or $\geq$ 1.5mm of upsloping ST depression] was evident on the rest or exercise ECG, this excluded the individual from study participation. If ischemia could not be determined by the exercise stress test due to suboptimal heart rate achieved or

resting baseline ST segment changes, a nuclear imaging study or dobutamine stress echocardiogram was conducted.

After determining the absence of myocardial ischemia, a single dose of sildenafil (50 mg) was ingested by the participants in the clinic setting. Their blood pressure was monitored by an ambulatory blood pressure monitoring system (Del Mar Pressurometer-model P6 – Del Mar Avionics, Irvine, California) for a period of 1 hour pre-dose and 4 hours post-dose (15-minute intervals). A post-dose fall of more than 10 percent in mean arterial pressure (seated, at rest for 5 minutes) sustained for more than 30 minutes and/or associated with hypotensive symptoms (dizziness, angina, diaphoresis) would make the individual ineligible for randomization into the trial. This measure determined intrinsic maintenance of hemodynamic stability. It may not have reflected physical state prior to sexual activity in the home environment. This threat could not be eliminated, only acknowledged by the investigators.

These safety measures were not repeated at any point apart from randomization, as the half-life of sildenafil is 4 hours hence no long-term improvement in exercise or prolonged hypotensive effect was expected with occasional ingestion. The schematic diagram of the safety protocol is illustrated in Figure 4.

All participants were given a wallet card with phone numbers for 24-hour contact with study personnel if the need to use nitroglycerine or adverse medication effects became a concern.

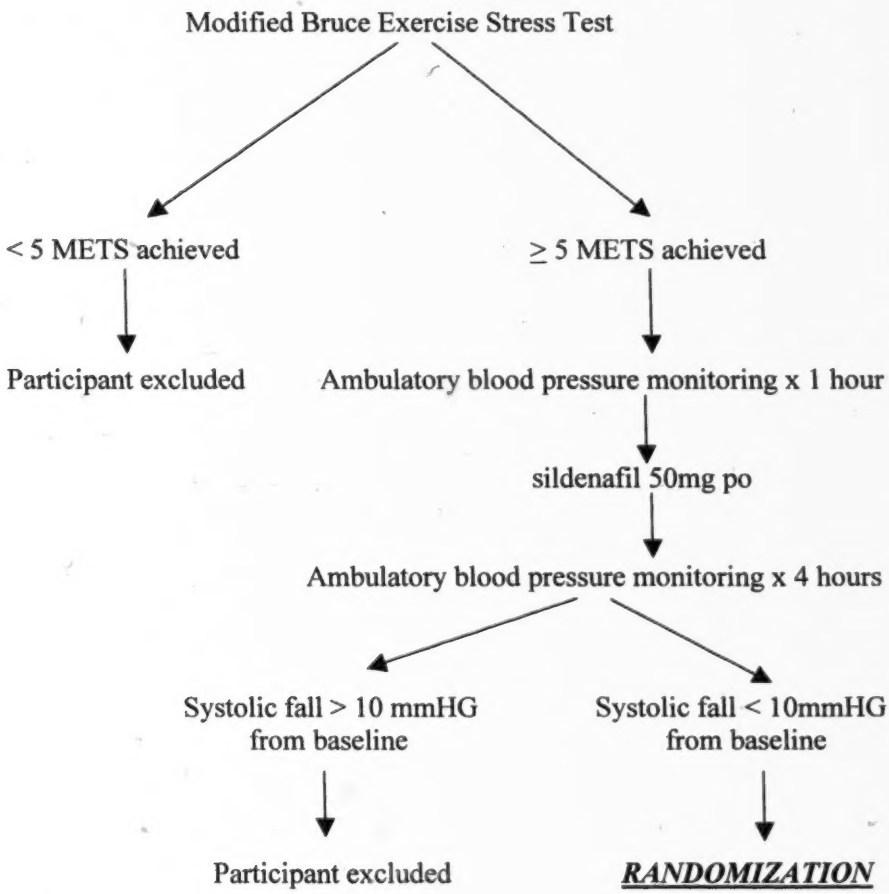


Figure 4. Study I: safety protocol algorithm.

Efficacy of Erectile Function Protocol

Erectile function was assessed at baseline, week 4 and week 10 using the domain of efficacy of erectile function of the IIEF. The IIEF questions respondents about their sexual function in the previous four weeks (see Figure 5 for the questions assessing efficacy of erectile function) (see Appendix F for the complete IIEF). It was developed during the MMAS and consists of fifteen questions that address the following four domains: efficacy of erectile function, achievement of orgasm, sexual desire, and satisfaction with intercourse. Each question is rated on a scoring scale from 1-5 with the raw scores added for statistical analysis (Michelakis, Tymchak, & Archer, 2000). It is a well-validated, multidimensional, self-administered questionnaire used for the clinical assessment of erectile function (Rosen et al., 1997). This tool has been validated across ten languages with consistently sound psychometric properties (Rosen et al., 1997). Rosen et al. (1997) concluded that this screening tool illustrated strong internal consistency between measured domains as well as adequate test-retest reliability citing 0.73 – 0.91 in the domain of erectile function. The IIEF has demonstrated a high degree of sensitivity and specificity to the effects of erectile dysfunction treatment ($p < 0.0001$) (Rosen et al., 1997).

Study II: Assessment of Depression

The BDI and CES-D were given to the participants at baseline, the conclusion of week 4 and the conclusion of week 10. These screening tools were administered before, rather than at, crossover and study termination because of a concern that participants may have been biased by change of treatment. The indexes were completed by the participants in a room in which they were not distracted nor interrupted. They were

OVER THE PAST FOUR WEEKS

Q1.	How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never
Q2.	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time 5 = Almost always / always
Q3.	When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never / never
Q4.	During sexual intercourse, *how often* were you able to maintain your erection after you had penetrated (entered) your partner?	2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time 5 = Almost always / always
Q5.	During sexual intercourse, *how difficult* was it to maintain your erection to completion of intercourse?	1 = Did not attempt intercourse 2 =Very difficult 3 = Extremely difficult 4 = Slightly difficult 5 = Not difficult
Q15.	How would you rate your *confidence* that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

Figure 5. International index of erectile function: items of the efficacy of erectile domain.

allotted was much time as needed in order to complete the questionnaires. Opportunity to discuss the questionnaires and their responses was offered once the questionnaires had been complete. Participants who were found to have total scores at or above cutoff on either of the depression indices (BDI $\geq$11, CES-D $\geq$ 16) on any testing occasion were referred to a psychologist for diagnostic interviews using DSM-IV (American Psychiatric Association, 2000) criteria.

BDI

The BDI consists of twenty-one questions that investigate four categories of depressive symptoms including emotion, cognitive ability, motivation, and physical symptoms (Golin & Hartz, 1979). Copyright limitations do not allow the inclusion of the scale in this thesis. Each question is scored on a scale from 0 to 3 depending on the intensity experienced in the two weeks previous. The individual scores are added and the total score is used for evaluation. Scores < 11 indicate normal, 11-16 mild mood disturbance, 17 – 20 borderline depression, 21 – 30 moderate depression, 31 – 40 severe depression, and 40+ extreme depression (Schotte, Maes, Cluydts, De Doncker, & Cosyns, 1997).

The complete scale cites reliability coefficients within fifteen non-psychiatric samples as exhibiting a mean alpha of 0.81 (Ambrosini, Metz, Bianchi, Rabinovich, & Undie, 1991) (range of 0.73 – 0.92). In non- psychiatric populations, the content validity (the correlation between clinical and questionnaire findings) was cited as a mean alpha of 0.60 (Bonin-Guillaume, Clement, Chassain, & Leger, 1995) (range of 0.55 – 0.73).

A shortened form of thirteen questions was developed, though little validation information exists. Reynolds and Gould (1981) brought the condensed version measures

of reliability into question. A meta-analysis of five studies revealed low validity scores of the shortened version. These trials assessed depressed adolescents (Bennett et al., 1997), chronic pain sufferers (Chibnall & Tait, 1994), bereaved adults (Leahy, 1992), and the elderly (Foelker & Shewchuk, 1992; Scogin, Beutler, Corbishley, & Hamblin, 1988). Borderline reliability results were cited in all trials, concluding that careful consideration be exercised with regards to applicability to the population under study. Compared to the short form, the complete BDI was deemed to provide the most accurate assessment of depressive symptoms in this population.

CES-D

The CES-D is a twenty item, self report instrument that is a widely used screening tool that designates depressed and non-depressed subjects in clinical studies (Appendix G). Individual values of each question are added to determine a total score. The CES-D scores can range from 0 – 60. The cut-off to identify those with clinically relevant symptoms of depression is 16 (Araujo et al., 1998; Beekman, Penninx et al., 1997; Weissman, Pottenger et al., 1977; Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977). Although a higher cut-off score of > 21 has been utilized by some trials, this was for the assessment for the presence of clinical depression (Lyness et al., 1997; Williams et al., 2002). It is typically used in the non-psychiatric population. It is widely used in elderly populations and has been found to have good psychometric properties in this population (Himmelfarb & Murrell, 1983; Kinzie, Lewinsohn, Maricle, & Teri, 1986). It is an internally consistent, valid measurement tool that assesses for depressive symtomatology with emphasis on depressed mood (Beekman, Deeg et al., 1997; Lyness et al., 1997). The cited sensitivity and specificity are 0.806 and 0.534 respectively

(Lyness et al., 1997). It is particularly useful in detecting depressive symptoms in high-risk groups (Duer, Schwenk, & Coyne, 1988), such as those with chronic illness. Thus it was felt that this index would be appropriate for those with heart failure and erectile dysfunction.

Ethical Considerations

Approval of Study I was obtained through the Research Ethics Board (Panel A) at the Capital Health in January 2001 (see Appendix H). The Research Ethics Board approved Study II in March 2001 (see Appendix I), as an addendum (see Appendix J) to the original protocol, before data collection.

All participants were informed about the purpose of the study, study procedures, and potential risks, benefits, and side effects to participation and participation required a signed consent form. They were informed of the potential improvement to erectile function as well as the assessment of psychological effects (BDI and CES-D), and the assessment of physical symptoms (LIhFE). Benefits to study participation included the opportunity to utilize sildenafil in the environment of close monitoring by study staff, inclusive of physicians. Risks were limited to rhythm disturbances during the EST and symptomatic hypotension caused by the ingestion of sildenafil. The initial monitoring in the hospital environment following ingestion of the initial dose of sildenafil 50 mg minimized both of these risks. Other potential side effects mentioned may have included headache (16%), flushing (10%), upset stomach (7%), nasal congestion (4%), urinary tract infection (3%), abnormal vision, color tinges, blurred vision (3%), diarrhea (3%), dizziness (2%), and rashes (2%) (Langtry & Markham, 1999). While these effects may be unpleasant, they are not physiologically life threatening and usually subside with the

discontinuation of treatment. It was considered that since the medication had not been previously used in patients with moderate congestive heart failure, the prevalence and safety of these side effects could be assessed.

If a participant scored above the cutoff values of the depression indexes, the participant was referred for a diagnostic interview with the outpatient psychology service to further investigate the presence and severity of clinical depression. The psychologist did not interview participants that screened negative on both indexes. A single experienced psychologist conducted these diagnostic interviews.

Participants were given the opportunity to ask questions of the investigators and discuss concerns at any point during the study. Upon deciding to participate, they were given the written information sheet. The consent was voluntarily, and signed and dated by both the subject and a witness.

Data collected for the purpose of this study is being kept in a locked filing cabinet in a secure office. Only study investigators and study staff have access to data. Participants were identified only by their initials and an individual study number. This data will be stored for 7 years beyond the conclusion of the trial.

The final results of the study are being compiled for published manuscript upon completion of data collection and subsequent analysis.

Statistical Analysis

Sample Size Calculation

The sample size for the primary trial was calculated using treatment effect size estimates derived from the literature (Goldstein et al.,1998). They noted an increase in mean IIEF difference from 12 to 20. It was decided by the research team to accept a

standard error of the mean (SEM) of 2 to allow for a range of variation that may be present given a population with a confounding disease process (Appendix J).

The calculations resulted in the following sample size selection:

$\alpha = 0.01$ Power = 0.81 SEM = 2

The formula for calculation of sample size can be found in Appendix K.

These parameters resulted in a calculated sample size of 39 participants per study group, in this case as participants served as their own controls, each person would participate in each arm, and hence roughly 39 patients would be enrolled. The effect size chosen for this population is less than previously indicated as studies in which this was evidenced studied males with primary erectile dysfunction of unknown etiology. This lower effect size was accepted as current knowledge indicates that congestive heart failure is a known cause of erectile dysfunction and this study is not designed to affect the treatment of congestive heart failure in any way. Attrition was included in the original sample size calculations, but all males that enrolled in the study completed all protocol procedures (allowing us to use a smaller sample size than calculated).

Data Analysis

The degree of variance of baseline characteristics between the groups was determined using chi square analysis and basic t-tests where appropriate. As every patient served as their own control, data from the two groups was compared at baseline, week 4, and week 10 using a 2 x 3 (two treatment groups at three assessment periods) repeated measures ANOVA. Post-hoc analysis used Fisher's probable least-significant differences test (Statview, SAS Institute). The final data was expressed as a mean $\pm$ standard error of the mean (*SEM*). A $p<0.05$ was considered statistically significant.

CHAPTER 4

Results

The purpose of this chapter is to present the results of Study II. The characteristics of the participants will be described, followed by a presentation of the findings relative to: 1) the relationship between depressive symptoms and the efficacy of erectile function in males with moderate heart failure treated with sildenafil and placebo and, 2) the comparison of the BDI and CES-D as screening tools for depression in males with moderate heart failure.

Participant Characteristics

Over the period of March 2001 to June 2002, thirty five men with congestive heart failure (NYHA Class II-III) were enrolled in Study 1 & Study 2. Twenty-five (71%) of the men had NYHA Class II and ten (29%) of the participants had NYHA Class III. Their mean ($\pm$ *SEM*) age was 60 $\pm$ 2, with an age range of 36 to 74. These participants represented a convenience sample of males currently attending the biweekly Heart Function Clinic at the study center. All participants completed the twelve-week protocol. Table 2 describes the clinical characteristics of this sample.

A comparison of baseline characteristics of the participants randomly assigned to the two groups (placebo first/sildenafil first), using chi square or independent t test analysis, where appropriate, revealed that both groups were homogeneous with regards to NYHA classification, age, medications, co-morbidities and etiology of congestive heart failure. No statistically significant differences existed between the two groups on any of the variables. The results of chi square analysis and paired t-test are found in Table 3.

Table 2

Participants Demographic and Clinical Characteristics (Sildenafil First and Placebo First)

Characteristic	Number (n = 35)		%	Mean ± *SEM*	
	Sildenafil First	Placebo First		Sildenafil First	Placebo First
Age				61±3	60±2
Functional Capacity					
NYHA Class II	14	11	(40) (31)		
NYHA Class III	3	7	(9) (20)		
Etiology					
Coronary Artery Disease	9	12	(26) (34)		
Idiopathic	5	4	(14) (11)		
Other	3	2	(9) (6)		
Concurrent Conditions					
Diabetes	4	5	(11) (14)		
Hypertension	12	12	(34) (34)		
Medications					
ACE Inhibitors	16	17	(46) (49)		
βeta blockers	16	17	(46) (49)		
Diuretics	16	15	(46) (43)		
Acetylsalicylic acid	8	14	(23) (40)		
Coumadin	13	9	(37) (26)		
Digoxin	12	10	(34) (29)		
Calcium channel blockers	3	1	(8) (3)		

Table 3

Statistical Analyses Comparing the Baseline Characteristics of the Treatment Groups (Sildenafil First and Placebo First)

Baseline Characteristics	Chi square	Independent t test
Age		$t(95) = .162, p = .87, d = .60$
NYHA Classification	$\chi^2(1, N = 35) = 1.93, p = .16$	
Etiology	$\chi^2(1, N = 35) = 5.17, p = .27$	
Concurrent Conditions		
Diabetes	$\chi^2(1, N = 35) = .08, p = .77$	
Hypertension	$\chi^2(1, N = 35) = .06, p = .80$	
Medications		
ACE Inhibitors	$\chi^2(1, N = 35) = .002, p = .97$	
βeta-blockers	$\chi^2(1, N = 35) = .002, p = .97$	
Diuretics	$\chi^2(1, N = 35) = 1.01, p = .32$	
Acetylsalicylic acid	$\chi^2(1, N = 35) = 3.53, p = .06$	
Coumadin	$\chi^2(1, N = 35) = 2.62, p = .11$	
Digoxin	$\chi^2(1, N = 35) = .85, p = .36$	
Calcium channel blockers	$\chi^2(1, N = 35) = 1.26, p = .26$	

The Relationship of Depressive Symptoms and Erectile Dysfunction in Males with Congestive Heart Failure Before and After Treatment

A summary of each participant's total scores on the IIEF, BDI, and CES-D will be presented in this section. The relationship between erectile dysfunction and depressive symptoms was assessed by comparing the trend of improvement or deterioration of the IIEF (the six questions from the domain of efficacy of erectile function domain) with the scoring trends from the BDI and CES-D. Severity of reported scores from each depression index will conclude the results reported in this section. Depressive scores will also be considered from a clinical standpoint.

Summary of IIEF, BDI and CES-D Scores

Table 4 presents the total scores of each of the 17 participants who received sildenafil as their first treatment at the three predetermined time intervals on the IIEF, the BDI, and the CES-D. The shaded areas indicate scores above the screening cut-off indicating a positive screen. Table 5 summarizes these scores by presenting the range as well as the means $\pm$ *SEM*.

Table 5

Index scores at Baseline, Week 4 and Week 10 [Range (Means $\pm$ SEM)] – Sildenafil first.

n = 35

	Baseline	Week 4	Week 10
IIEF	2-21 (9$\pm$1)	8-26 (15$\pm$1)	4-22 (10$\pm$1)
BDI	1-21 (9$\pm$1)	1-22 (6$\pm$1)	1-24 (8$\pm$1)
CES-D	0-12 (5$\pm$1)	0-9 (3$\pm$1)	0-12 (4$\pm$1)

Table 4

Total Scores (IIEF, BDI, CES-D) at Baseline, Week 4 and Week 10 – Sildenafil First

ID#	Baseline			Week 4			Week 10		
	IIEF	BDI	CES-D	IIEF	BDI	CES-D	IIEF	BDI	CES-D
2	7	21	16	15	22	10	5	24	13
3	14	7	3	14	4	3	12	14	5
6	8	10	6	13	6	3	11	6	4
10	2	1	6	12	1	2	6	1	3
11	6	10	6	8	3	2	6	6	2
14	1	6	4	12	2	1	6	2	1
15	6	9	3	12	10	3	8	9	4
17	21	10	6	22	9	4	21	6	6
18	4	9	4	15	3	1	5	11	5
19	10	3	1	18	4	0	10	2	1
22	2	15	12	9	9	6	4	14	12
23	9	5	3	10	4	0	4	9	6
26	15	10	8	16	6	4	13	10	9
30	16	5	0	26	3	0	13	4	0
31	12	16	9	13	9	9	10	13	6
34	16	7	2	23	8	4	22	5	0
35	9	8	3	17	4	3	11	5	2

Table 6 presents the total scores of the eighteen participants who received placebo as their first treatment at the three predetermined time intervals on the IIEF, the BDI, and the CES-D. Table 7 presents the summary data can be examined in the following chart as illustrating the range as well as the means $\pm$ *SEM*:

Table 7

Index scores at Baseline, Week 4 and Week 10 [Range (Means $\pm$ SEM)] – Placebo

n = 35

	Baseline	Week 4	Week 10
IIEF	2-20 (9$\pm$1)	4-15 (9$\pm$1)	8-30 (16$\pm$1)
BDI	4-25 (9$\pm$1)	4-32 (10$\pm$2)	1-16 (6$\pm$3)
CES-D	1-12 (6$\pm$1)	0-17 (6$\pm$1)	1-6 (3$\pm$<1)

Efficacy of Erectile Function (IIEF) – Results

Sildenafil, but not placebo significantly improved erectile function. Specifically: In the sildenafil first group $F(2,16) = 30.630$, sildenafil improved IIEF scores compared to both baseline ($p<0.0001$) and placebo ($p<0.0001$). In the placebo first group $F(2,17) = 37.567$, placebo did not alter IIEF scores, but sildenafil again improved erectile function ($p< 0.0001$ versus baseline and $p< 0.0001$ versus placebo) (see Figure 6). Slight improvement of efficacy of erectile function scores was evident when the scores of baseline and those reported during placebo treatment were compared (sildenafil first, $p<0.9069$, placebo first, $p<0.3311$).

Table 6

Total Scores (IIEF, BDI, CES-D) at Baseline, Week 4 and Week 10 – Placebo First

ID#	Baseline			Week 4			Week 10		
	IIEF	BDI	CES-D	IIEF	BDI	CES-D	IIEF	BDI	CES-D
1	4	11	8	4	11	11	28	7	5
4	20	7	6	12	4	9	28	1	2
5	12	4	2	15	4	5	18	2	2
7	11	8	8	11	9	7	15	9	4
8	8	25	17	10	32	12	14	16	7
9	2	10	8	6	9	14	12	6	2
12	10	8	8	10	4	4	18	4	4
13	17	4	11	15	9	5	30	5	1
16	8	8	2	10	7	2	16	4	1
20	5	14	12	7	17	17	14	10	4
21	10	9	7	11	6	5	17	7	4
24	6	8	6	5	10	6	12	6	2
25	9	7	2	11	8	2	16	5	2
27	2	12	9	4	10	6	8	8	6
28	5	9	6	5	10	6	10	7	3
29	12	6	1	12	5	2	18	5	1
32	9	5	5	9	5	9	12	5	6
33	3	10	4	4	8	2	10	4	2

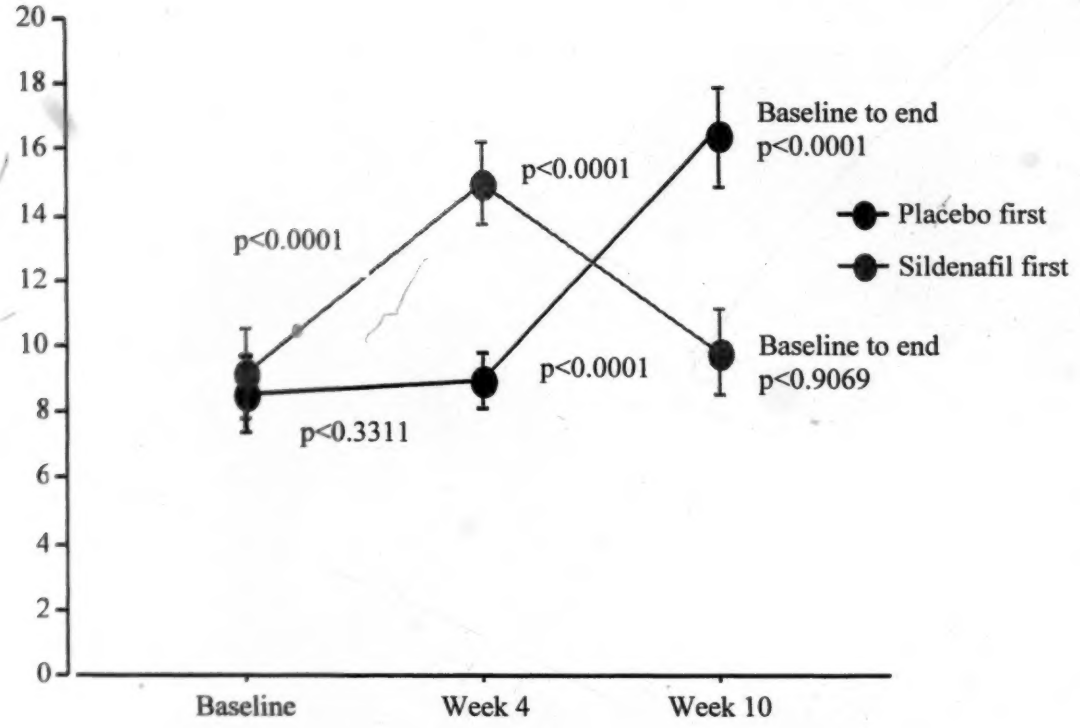


Figure 6. Total Scores of IIEF (efficacy of erectile function domain) at baseline, week 4 and week 10

Treatment of Erectile Dysfunction and BDI Scores - Results

Sildenafil, but not placebo significantly improved scores reported on the BDI. Specifically: In the sildenafil first group $F(2,16) = 5.011$, $p < 0.0128$, sildenafil improved BDI scores compared to both baseline ($p<0.0055$) and placebo ($p<0.0217$). In the placebo first group $F(2,17) = 10.089$, $p < 0.0004$, placebo did not alter BDI scores, but sildenafil again improved BDI scores ($p< 0.0025$ versus baseline and $p< 0.0001$ versus placebo) (see Figure 7). The interaction effect of treatment group x timing of sildenafil treatment was statistically significant in both groups.

In the sildenafil first group, comparison of baseline scores to those reported during the period of placebo indicated a minimal improvement. This decrease did not achieve statistical significance ($p<0.5741$). In the placebo first group, a mild worsening of depressive scores was evident between the periods of baseline to placebo, although failed to achieve statistical significance ($p<0.3103$).

Treatment for Erectile Dysfunction and CES-D Scores - Results

Sildenafil, but not placebo significantly improved scores reported on the CES-D. Specifically: In the sildenafil first group $F(2, 16) = 5.442$, $p < 0.0108$, sildenafil improved CES-D scores compared to both baseline ($p<0.0033$) and placebo ($p<0.0434$). In the placebo first group $F(2, 17) = 6.186$, $p < 0.0068$, placebo did not alter CES-D scores, but sildenafil again improved CES-D scores ($p< 0.0030$ versus baseline and $p< 0.0122$ versus placebo) (see Figure 8). The interaction effect of treatment group x timing of sildenafil treatment was statistically significant in both groups.

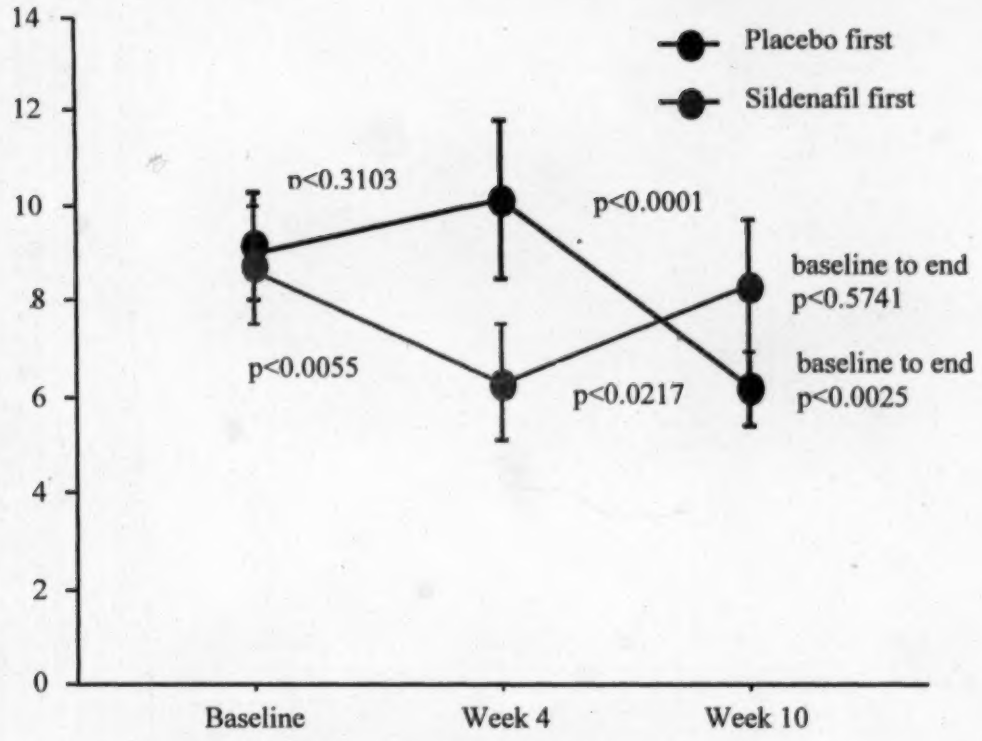


Figure 7. Total scores of BDI at baseline, week 4, and week 10.

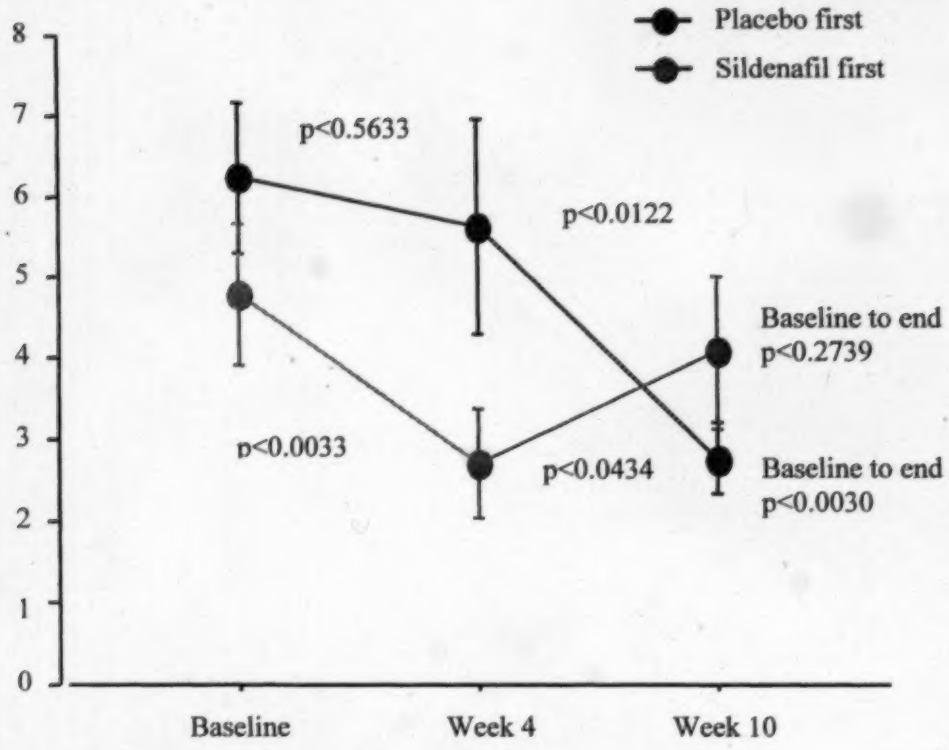


Figure 8. Total scores of CES-D at baseline, week 4, and week 1.

Both groups showed minor improvement of scores between baseline and those reported during periods of placebo (sildenafil first, $p<0.2739$, placebo first, $p<0.5633$). This improvement failed to achieve statistical significance

Severity of Depressive Symptoms

Having considered the depressive symptom profiles in the two treatment groups from a statistical standpoint, the BDI depressive symptom profiles of the participants were considered from a clinical standpoint using symptom severity (see Table 8). The clinical indicators of scores above the cutoff, indicating severity of symptoms beyond normal levels, were referred on to psychological assessment for the presence of clinical depression.

As can be seen from Tables 4 and 6, participants 2, 3, 22, and 31 in the sildenafil first group and participants 1, 8, 20, and 27 in the placebo first group reported depression scores above cutoff one or more times. In the sildenafil first group, thirteen participants (76%) consistently reported scores that were not indicative of symptoms of depression. Three (18%) participants in this group indicated mild mood disturbance, two (12%) of which screened positive at baseline and week 10, while one (6%) participant only screened positive for depressive symptoms at week 10 during the placebo treatment period. One (6%) participant in this group consistently scored in the range indicative of moderate depression throughout all screening assessments regardless of current treatment.

In the placebo first group, fourteen participants (77.5%) consistently reported scores that were not indicative of symptoms of depression. Five (28%) participants in this group indicated mild mood disturbance, three (12%) of which screened positive at

Table 8

Severity of Depressive Symptoms: Total BDI scores [Number (Percentage of Treatment Group)] by Treatment Group (Sildenafil first and Placebo first) at Baseline, Week 4 and Week 10

Range	Severity of Depressive Symptoms	Total Score Treatment Week					
		Sildenafil first (n = 17)			Placebo first (n = 18)		
		0	4	10	0	4	10
1-10	Not depressed	14 (82)	16 (94)	13 (76)	14(77.5)	15 (83.5)	17 (94.5)
11 - 16	Mild mood disturbance	2 (12)	0 (0)	3 (18)	3 (17)	1 (5.5)	1 (5.5)#
17 - 20	Borderline depression	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.5)	0 (0)
21 - 30	Moderate depression	1 (6)*	1 (6)*	1 (6)*	1 (5.5)#	0 (0)	0 (0)
31 - 40	Severe depression	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.5)#	0 (0)
40 +	Extreme depression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note. * Participant 2, # Participant 8

baseline, one (5.5%) of which continued to report symptoms of depression at week 4. Neither of these participants reported depressive symptoms at week 10 during the period of sildenafil treatment. One (5.5%) participant in this group scored in the range indicative of moderate depression at baseline and indicated severe depression at week 4 by reporting higher scores than previous. By week 10, this participant had improved to a level of mild mood disturbance following treatment with sildenafil.

Comparison of the BDI and CES-D as Screening Tools for Depression in Males with Moderate Heart Failure

The second purpose of this thesis was to compare the BDI and CES-D as screening tools for depression in males with moderate heart failure. The BDI results will be presented first, followed by those of the CES-D. Concordance and disagreement between the indexes will be presented. The participants that screened positive for depressive symptoms were referred to the psychologist will be discussed as well as the results of these diagnostic interviews. The BDI and CES-D results with the removal of scores based upon the removal of somatic questions from the reported total score will also be presented.

Concordance between the BDI and CES-D

The concordance and disagreement between the BDI and the CES-D was determined by examining the participants in who the separate index scores indicated similar results and in who they varied. The screening results of the two indexes will be examined simultaneously with regards to the concordance and disagreement

The BDI and the CES-D both screened 27 (77%) participants as negative for symptoms of depression. This was consistent over all periods of assessment. Absence of clinical depression was not confirmed with diagnostic interview.

The BDI and CES-D did not show consistent agreement with regards to positive screens except for two (6%) participants at the baseline assessment (see Table 9). These participants that were identified by the CES-D as indicating depressive symptoms at baseline were the same participants that the BDI identified as reporting depressive symptoms in all three assessments. In total, the BDI and CES-D agreed on the depressive screening of 29 (83%) participants (2 positively screened, 27 negatively screened).

Referral for Diagnostic Assessment

After the individual participants completed the depression screening indexes, participants who screened positive for having depressive symptoms, on either index, were referred for a diagnostic interview with a psychologist. This interview assessed for the presence of clinical depression. This referral occurred with the first score reported that was indicative of depressive symptoms by the indexes. The mean time to diagnostic interview was four days with a range of one to seven days. All participants that screened positive for depressive symptoms were not found to have clinical depression during the assessment interview, though their number of depressive symptoms (DSM-IV criteria) were not reported.

Effect of Somatic Symptoms on Depressive Index Scores.

As the participants who screened as positively reporting depressive symptoms on both the BDI and the CES-D were not found to be clinically depressed given the results of an assessment interview by a psychologist, a question was raised regarding the

Table 9

Summary of Participant's Positive Screening Scores (total) by Reporting Period, Treatment and Depressive Index Scores (darker shaded areas indicate scores in which both indexes showed concordance)

	Period of Assessment					
	Baseline		Week 4		Week 10	
Participant	BDI	CES-D	BDI	CES-D	BDI	CES-D
1	11	8	11	11	7	5
2	21	16	22	10	24	13
3	7	3	4	3	24	13
8	25	17	32	12	16	7
20	14	12	17	15	10	4
22	15	12	9	6	14	12
27	12	9	10	6	8	6
31	16	9	9	9	13	6

Note: Two (6%) participants in which the indexes indicated concordance agreement between the indexes at baseline.

influence of the somatic items. It is known that the congestive heart failure population has confounding organic disease pathology and their physical limitations may skew depressive index scores toward false positive values. The responses to the somatic items [BDI (#15, #16, #17, #18, #19)][CES-D (questions # 2, #11, #19)] were removed from each index and the totals were reprocessed. The results of this recalculation process are shown in Tables 10 and 11. Figures 9 and 10 illustrate the effect of erectile function on the recalculated scores of the respective indexes.

This recalculation with the scores from the somatic items eliminated, removed some, though not all, of the participants from the group who previously screened positive for significant levels of depressive symptoms. Four (11%) participants now screened positive for depressive symptoms in the BDI. The two (6%) participants that had previously reported scores as positive for depressive screens on the CES-D became excluded from this group.

Treatment of Erectile Dysfunction and BDI Scores (Somatic Items Omitted) – Results.

Sildenafil, but not placebo significantly improves scores reported on the BDI with the somatic scores removed. Specifically: In the sildenafil first group $F(2,16) = 4.889$, $p < 0.0139$, sildenafil improved BDI scores compared to both baseline ($p<0.0037$) and placebo ($p<0.0094$). In the placebo first group $F(2,17) = 10.749$, $p< 0.0002$, placebo did not alter BDI scores, but sildenafil again improved BDI scores ($p< 0.0019$ versus baseline and $p< 0.0001$ versus placebo) (see Figure 10). The interaction effect of treatment group x timing of sildenafil treatment was statistically significant in both groups.

Table 10

Participants Scores (total IIEF, total BDI – somatic scores, total CES-D – somatic scores) at Baseline, Week 4 and Week 10 – Sildenafil First

ID#	Baseline			Week 4			Week 10		
	IIEF	BDI	CES-D	IIEF	BDI	CES-D	IIEF	BDI	CES-D
2	7	18	8	15	15	6	5	17	9
3	14	2	2	14	0	3	12	6	3
6	8	6	6	13	4	3	11	5	5
10	2	0	6	12	0	2	6	0	3
11	6	6	6	8	1	2	6	3	2
14	1	4	0	12	0	0	6	0	0
15	6	3	3	12	3	2	8	5	4
17	21	6	4	22	5	3	21	3	3
18	4	6	4	15	0	1	5	4	5
19	10	0	1	18	0	0	10	0	1
22	2	9	4	9	6	5	4	9	10
23	9	3	3	10	4	0	4	9	5
26	15	10	6	16	6	2	13	10	7
30	16	5	0	26	3	0	13	4	0
31	12	14	7	13	7	9	10	10	5
34	16	3	2	23	3	4	22	5	0
35	9	3	3	17	0	3	11	4	2

Table 11

Participants Scores (total IIEF, total BDI – somatic scores, total CES-D – somatic scores) at Baseline, Week 4 and Week 10 – Placebo First

ID#	Baseline			Week 4			Week 10		
	IIEF	BDI	CES-D	IIEF	BDI	CES-D	IIEF	BDI	CES-D
1	4	8	6	4	7	9	28	4	3
4	20	6	4	12	4	6	28	0	2
5	12	3	2	15	4	5	18	0	2
7	11	8	6	11	9	6	15	6	3
8	8	15	13	10	15	9	14	8	7
9	2	7	5	6	10	8	12	4	2
12	10	6	4	10	1	0	18	3	3
13	17	2	8	15	6	5	30	4	1
16	8	6	2	10	4	2	16	1	1
20	5	8	9	7	14	14	14	10	4
21	10	6	7	11	6	5	17	3	4
24	6	7	4	5	7	4	12	5	1
25	9	2	0	11	6	2	16	0	0
27	2	10	7	4	10	5	8	7	5
28	5	8	4	5	6	4	10	4	1
29	12	4	1	12	3	2	18	0	1
32	9	2	3	9	1	9	12	1	5
33	3	7	3	4	6	2	10	1	2

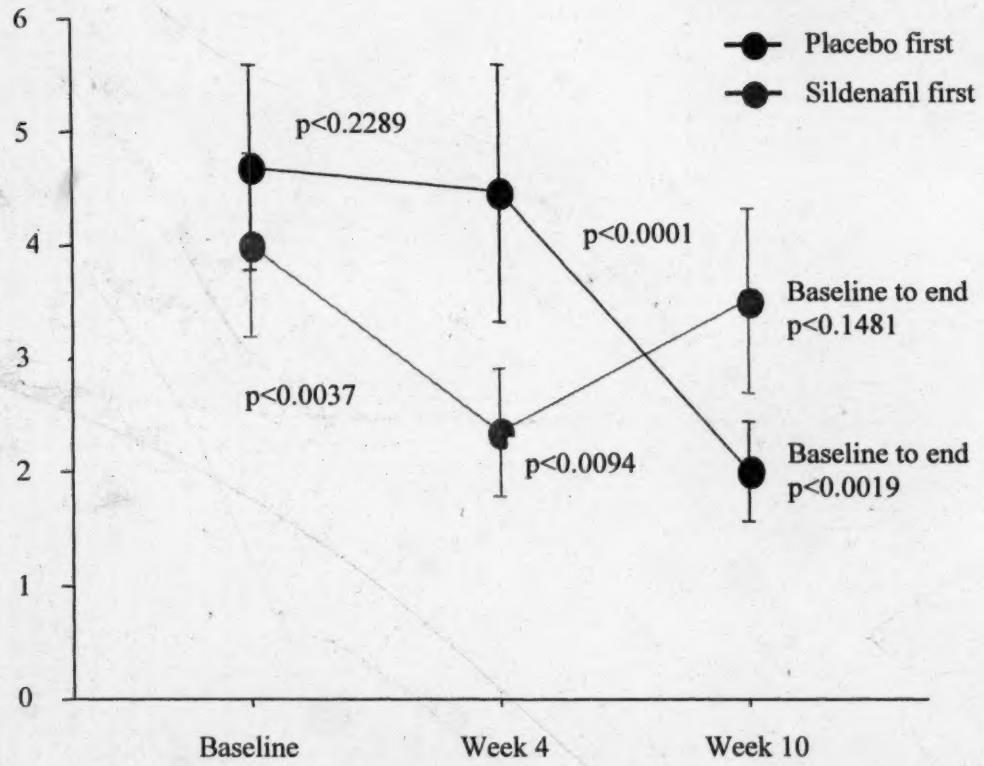


Figure 9. BDI scores (somatic questions omitted) at baseline, week 4, and week 10.

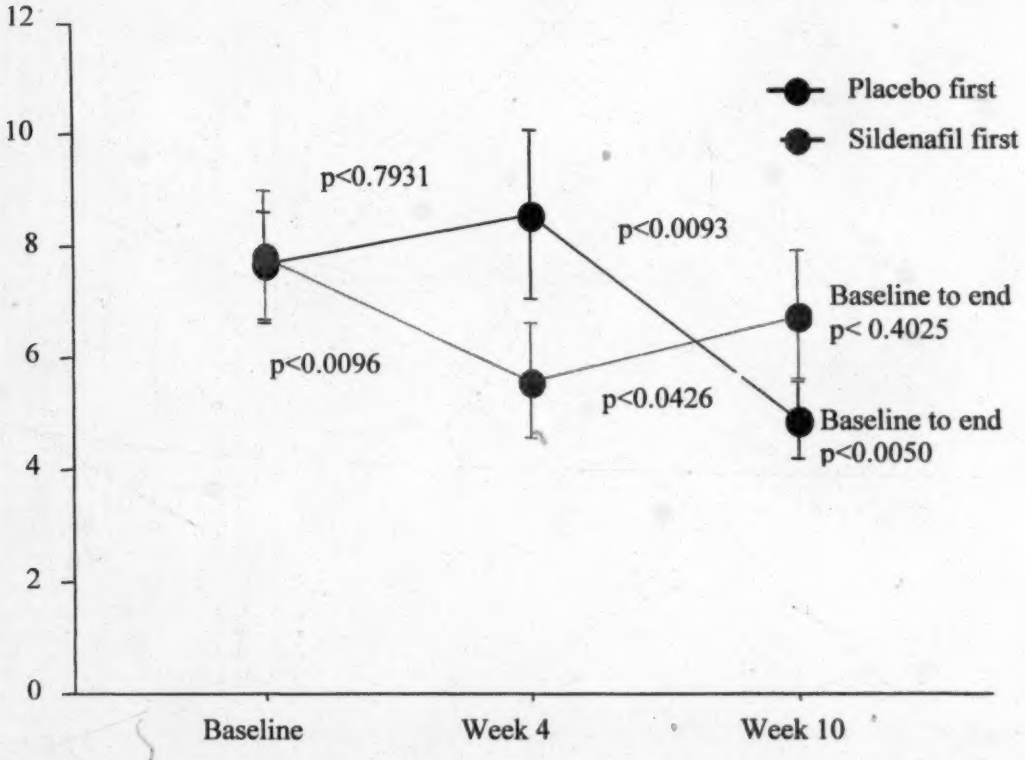


Figure 10. CES-D scores (somatic questions omitted) at baseline, week 4, and week 10.

Treatment of Erectile Dysfunction and CES-D Scores (Somatic Items Omitted) - Results.

Sildenafil, but not placebo significantly improves scores reported on the CES-with the somatic scores removed. Specifically: In the sildenafil first group $F(2,16) = 4.110$, $p < 0.0281$, sildenafil improved CES-D scores compared to both baseline ($p<0.0096$) and placebo ($p<0.0426$). In the placebo first group $F(2,17)= 5.883$, $p < 0.0083$, placebo did not alter CES-D scores, but sildenafil again improved CES-D scores ($p< 0.0050$ versus baseline and $p< 0.0093$ versus placebo) (see Figure 10). The interaction effect of treatment group x timing of sildenafil treatment was statistically significant in both groups. The comparison of baseline scores to those reported during the period of placebo in the sildenafil first group and the placebo first group indicated a minimal decrease. This decrease did not achieve statistical significance ($p<0.1481$ and 0.2289, respectively).

In the sildenafil first group, comparison of baseline scores to those reported during the period of placebo indicated a minimal improvement. This decrease did not achieve statistical significance ($p<0.4025$). In those that received placebo first a mild worsening of depressive scores was evident between the periods of baseline to placebo, though failed to achieve statistical significance ($p<0.7931$).

CHAPTER 5

Summary and Discussion

The twofold purpose of Study II was intended to: (1) investigate the relationship between depressive symptoms and erectile dysfunction in males with moderate congestive heart failure (NYHA Class II-III) before and after treatment with sildenafil, and (2) compare the BDI and CES-D as screening tools for clinical depression in males with moderate congestive heart failure (NYHA Class II-III). In this chapter, each purpose will be addressed separately. Limitations of the study will follow. The implications of the study for clinical practice and future research will also be addressed.

The Relationship of Depressive Symptoms and Erectile Dysfunction in Males with Congestive Heart Failure Before and After Treatment

Goldstein (2000) proposed that a relationship existed between erectile dysfunction and depression. In this study, as scores of the IIEF (efficacy of erectile function domain) increased (indicating erectile improvement), the scores on the depressive indexes decreased (indicating lower levels of depressive symptoms). The opposite reaction was also evident when participants who had initially received sildenafil crossed over to receive placebo. Their efficacy of erectile function scores decreased (indicating worsening erectile function) and their depressive index scores increased (indicating more depressive symptoms), returning to values reported at baseline.

Efficacy of Erectile Function

Improvement in erectile function experienced by these participants was attributed to sildenafil, as it was the only variable manipulated by the investigators during the time of the trial and efficacy of erectile function assessments. The very nature of the

congestive heart failure (vascular remodeling and medication profile) limits the possibility that erectile function would improve without medical intervention. No other therapeutic manipulation occurred concurrently.

The scores achieved on the efficacy of erectile function domain of the IIEF showed significant improvement during the period of treatment with sildenafil when compared to the baseline and during treatment with placebo. IIEF scores reported during treatment with placebo did improve slightly from the scores reported at baseline, though failed to achieve statistical significance. It is possible that a "placebo effect" took place as has been reported in previous trials with sildenafil. In these trials, 10% - 24% participants reported improvement of erectile function during treatment with placebo (Olsson & Persson, 2001; Price et al., 1998). This study witnessed a similar effect though not to the reported levels of past studies. Placebo effect is more commonly found in true randomized studies in which two groups participate, one of which gets only active treatment, the other receives only placebo. A true placebo effect may not be appropriately reported in a crossover study design as anticipation of active treatment may increase participant's sexual activity beyond previous frequency and elevate self-reports of improved function.

Clinical trial effect may also play a role in the improvement of index scores in that study participants typically report improvement on quality of life scales despite treatment protocol. This often can be attributed to the participants secure sense of being closely monitored by a medical professional and the altruistic feelings they experience about furthering scientific study by participating in a research protocol. In this instance, this improved sense of well-being may have contributed to improved erectile function.

This was the first study that had examined the efficacy of sildenafil in this chronically diseased population. The improvement of erectile function was similar to that found in other males with chronic medical conditions, both cardiac and otherwise (Kloner, 2000; Shabsigh, 1999).

Treatment of Erectile Dysfunction and Depressive Index Scores

The scores of the depression indexes improved as the IIEF (efficacy of erectile function domain) scores improved. The only variable actively manipulated by the investigators was the prescription of placebo or sildenafil therapy. It is known that many factors in day to day life also influence erectile dysfunction and depression (Meuleman, 2002; Seidman, 2002). Extraneous variables, which could affect either condition or both concurrently, are beyond the control of the investigator. An example of such a variable would include spousal conflict that may impair erectile function and exacerbate depressive symptoms. Two common clinical trial practices were undertaken in an attempt to limit the effect of these extraneous variables. First, randomization into the two treatment groups sought to make the effects of extraneous influence equal between the treatment groups. The demographic profile of the two treatment groups in this study was homogeneous. Secondly, the crossover design allowed the participants to serve as their own control thereby limiting demographic and clinical characteristic differences to time effects as opposed to participant variance.

The ability of the individual indexes to determine the severity of depressive symptoms is precarious at best. Screening tools are meant to determine the level of probability that a condition is absent or present (Singh & Newton, 2002). It cannot

determine the extent to which that symptom (set of symptoms) is present. The CES-D does not seek to assess severity, only the presence or absence of depressive symptoms.

The BDI does attempt to address the severity of depressive symptoms by separating scores into six categories of increasing severity ranging from not depressed to extreme depression. Most participants consistently scored in the "not depressed" category throughout all assessments. No participant achieved scores in the extreme depression category. The severity of the BDI is not usually a component of assessment on the original screening, as clinically, it only mandates a score of > 21 to indicate a person as having a high degree of probability that they are experiencing a clinical depression. The levels of depressive symptoms are used as a method of tracking treatment response after the diagnosis of clinical depression is confirmed.

Twenty seven (77%) participants consistently reported scores in the lowest range of depressive symptom severity (ie., not depressed). The next group of six (17%) patients reported scores of mild mood disturbance once or twice over the three assessments. Interestingly, one participant (#3) (sildenafil first group) reported a single score of mild mood disturbance after treatment with placebo. He did not report scores of significance prior to this time.

In this study two participants (#2 and #8) reported scores indicative of depressive symptoms across all three points of assessment. Participant #2 was randomized into the sildenafil first group. He consistently reported scores in the range of moderate depression across all assessments, regardless of current treatment for erectile function. The psychological assessment did not classify him as clinically depressed following the

diagnostic interview. This man died 7 months after study participation in the hospital with complications of congestive heart failure. His wife and family were by his side.

Participant #8 was randomized into the placebo first group. Initially, he reported scores of moderate depression and reported scores in the range of severe depression during treatment with placebo. His severity of depressive symptoms significantly improved, reporting in the range of mild mood disturbance during the treatment with sildenafil.

Comparison of the BDI and CES-D as Screening Tools for Depression in Males with Moderate Heart Failure

Case identification of patients with clinical depression is the key to successful treatment. In other words, we must be alert to patient's signs of depression if we are to optimize their psychological state and assist them in coping with the prognosis of chronic illness. The two steps involved in case identification are screening and diagnostic interview/assessment. Screening for depression and depressive symptoms can be completed with the utilization of reliable and well-validated screening tools. The best method for diagnostic assessment is interview by qualified professionals (psychologists or psychiatrists) using criteria provided by the American Psychological Association (DSM-IV criteria). This study utilized appropriate screening tools (BDI and CES-D) and referral for depression assessment (psychologist using DSM-IV criteria for MDE and dysthymia).

The BDI reported a total of eight (23%) participants as experiencing depressive symptoms, one of which consistently scored in the moderately depressed range. The CES-D showed concordance with the BDI on two (6%) of these participants. The two

participants in whom the BDI and CES-D did show concordance, as positive screens for depressive symptoms were the men that the BDI consistently reported as depressed across all assessment periods. This consistency of scores across time should alert the clinician to routinely evaluate the status of depressive symptoms in these individuals regardless of the findings from diagnostic interviews. It is alarming to realize that had only the CES-D been utilized, these males' single scores of significance may have been dismissed and not evaluated on an ongoing basis.

In addition to the two participants that screened positive, 27 (77%) participants screened negative with regards to depression/significant depressive symptoms in both indexes. There were six (17%) participants who the BDI screened as positive once or twice during the course of assessments and the CES-D screened as negative across all assessments. This represents the total number of participants in who the indexes directly disagreed.

Concordance between the indexes was reported in 29 (83%) of participants (2 positive screens and 27 negative screens). Disagreement between the indexes was reported in six (17%) of participants. A combination of these two assessments would likely ensure that no participant with depressive symptoms would go unrecognized.

The diagnostic assessments did not indicate any participant as being clinically depressed. These interviews were in disagreement with 8 (23%) reported scores of positive screens for depressive symptoms. There was no agreement with any of the positive screens. The psychologist did not interview the participants who reported negative screening scores hence there is no concordance or disagreement data is available

about the number of false negative screens in this population. In clinical settings, negative scores on depressive indexes do not warrant psychological evaluation.

The positive screening scores in Study II were found to be partially as a result of somatic questions given negative interviews conducted using DSM-IV criteria. Fewer participants achieved scores indicative of depressive symptoms/depression when somatic questions were omitted from final calculation. These results were in keeping with the literature. False positive results, as a result of extremely positive scores from somatic indicators have been reported previously in both the BDI (Roberts, Lewinsohn, & Seeley, 1991; Ruiz, Silva, & Miranda, 2001; Sullivan, Weinshenker, Mikail, & Bishop, 1995; Zich, Attkisson, & Greenfield, 1990), and the CES-D (Beekman, Deeg et al., 1997; Gerety et al., 1994; Papassotiropoulos & Heun, 1999; Roberts et al., 1991; Roberts & Vernon, 1983; Thomas, Jones, Scarinci, Mehan, & Brantley, 2001; Zich et al., 1990). Participants may score in the depressive range, but these scores can be a result of somatic symptoms and not from depressed mood. The BDI retained four (11%) of the positive screening scores when the somatic questions were omitted.

The CES-D excluded all participants from having depressive symptoms / depression when somatic items were removed from the summation of scores. A few studies have shown little effect of somatic symptoms on the CES-D. This is in sharp contrast to those previously mentioned. Beekman et al. (1997) conducted a study determining the use of the CES-D scale in an elderly population with varying degrees of health/illness. Their conclusions indicated satisfactory criterion validity in this group regardless of physical illness, cognitive decline, or anxiety. They found that the CES-D was able to identify depressive symptoms in those with confounding symptoms due to

other causes. Little overlap between depressive symptoms and those of somatic etiology was demonstrated in previous trials (Berkman et al., 1986), (Foelker & Shewchuk, 1992).

Another factor that may have contributed to the large number of false positive screening tests was the BDI cutoff score of 11. This score was used to screen for any degree of depressive symptoms. This cutoff score was found to be too low. The utilization of the clinical cutoff score of >21 would have provided more consistent findings with the CES-D. Diagnostic interview results would have shown strong concordance with the results of the BDI index utilizing this higher cutoff score. The CES-D reported two participants as screening positive for depressive symptoms when the entire index was scored. Both participants became negative screens with the removal of the scores from the items addressing somatic symptoms.

This variance of scores between scales and within the scales themselves, as shown by the significance of scores following the elimination of somatic items underscores the need to utilize these indices only as screening indexes for depression. Previous research suggests that the use of more than one scale for this purpose may deliver more reliable results in a population with confounding medical conditions (Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994).

Limitations of the Study

The two limitations of the study are the self-report assessment of the extent of erectile dysfunction experienced by the selected population and the cutoff scores utilized for the BDI.

Assessment of Erectile Dysfunction

The self-report method of erectile dysfunction may draw criticism in that it utilized a relatively newly constructed index (1997) to which there are no previous indexes to which it can be compared. Early analysis from several trials indicates adequate validation of the tool even though no comparator exists.

The assessment of erectile dysfunction was limited to the participant's anecdotal self-reports and scores reported on the IIEF. The subjective and sensitive nature of the focus may cause a participant to exaggerate or minimize treatment response due to the personal nature of the questions on the index.

Objective erectile function assessment could be undertaken in the form of penile tumescence. This would determine the clinical severity of erectile dysfunction. This method of assessment would also provide an objective measure of effect of treatment in both the active treatment and placebo groups addressing the concern of strong placebo effect in this population.

BDI Cutoff Score

The cutoff score of 11 was found to be too low as it screened eight (23%) participants as reporting depressive symptoms and all that were assessed as negative for clinical depression. A cutoff score of 21, as is clinically used, would provide more accurate assessments of true depressive states.

Implications for Clinical Practice

Awareness of the high prevalence rate of depression and erectile dysfunction in males with congestive heart failure has implications for treating these individuals in the clinic setting. The presence of this comorbity of conditions in this population greatly

influences their overall quality of life, frequently resulting in poor intimate relationships and impaired social functioning.

Assessment of depression in males with moderate congestive heart failure may prove difficult given the interplay and overlap of symptoms between comorbid conditions. In order to increase the accuracy of assessment, the clinician must ensure that the screening tool(s) utilized is appropriate for those with chronic underlying conditions. Both the BDI and the CES-D are useful in this population provided appropriate cutoff scores are utilized. The recommended level for this population would be BDI $\geq$ 21, and the CES-D $\geq$ 16. It would also be prudent for the clinician to examine the total scores and determine the influence that the somatic symptoms had on the final score of that index. If the somatic symptoms provided the basis for the majority of the reported score, then alteration of medication or treatment regime may warrant consideration before further assessment of depressive symptoms is undertaken.

The utilization of two indexes in screening for depressive symptoms in those with confounding medical conditions has been suggested by previous research (Moller et al., 1994). This may be useful in assisting the clinician with their screening assessment of an individual, however, the constraints of time in a clinic setting may preclude the action of delivering two indexes. From this study, it can be suggested that the CES-D may be more useful in this population. However, it has also been determined that the BDI can be as effectively utilized as a screening tool with the clinically accepted cutoff score of $\geq$21.

Future Research

Future research should focus on qualitative studies which could address the study questions of:

1. What are the subjective feelings of the male with congestive heart failure, erectile dysfunction and depressive symptoms?
2. What extraneous variables (including social relationships, life events, and exacerbation/decline of symptoms related to their medical condition) play a role in the exacerbation of erectile dysfunction and/or depression in males with heart failure?

Conclusion

A relationship between depressive symptoms and erectile dysfunction in males with moderate congestive heart failure (NYHA Class II-III) before and after treatment with sildenafil was found when the scores of the IIEF, BDI and CES-D were compared at three predetermined assessment periods. Comparison of the BDI and CES-D as screening tools for clinical depression in males with moderate congestive heart failure (NYHA Class II-III) showed agreement on 83% of participants (2 positive screens, 27 negative screens). The BDI screened more participants as positive for depressive screens warranting diagnostic assessment by a psychologist. Diagnostic interview with a psychologist failed to identify any participants as having clinical depression. When items pertaining to somatic symptoms were removed from the indexes, reported scores were lower than previous on both indexes. A higher BDI cutoff score of 21 would limit the effects of the somatic items on the scores of males with erectile dysfunction and heart failure as well as potentially screen those people with a higher likelihood of depression and depressive symptoms limiting the number of false positive results. The clinician must be aware of the impact that somatic symptoms can have on scores of indexes that incorporate these parameters.

References

Ambrosini, P. J., Metz, C., Bianchi, M. D., Rabinovich, H., & Undie, A. (1991). Concurrent validity and psychometric properties of the Beck Depression Inventory in outpatient adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(1), 51-57.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders - fourth edition (text revised)*. Washington, DC: R.R. Donnelly & sons Co.

Andersson, K., & Stief, C. (2000). Penile erection and cardiac risk: pathophysiologic and pharmacologic mechanisms. *American Journal of Cardiology, 86*(2A), 23F-26F.

Andersson, K. E., & Wagner, G. (1995). Physiology of penile erection. *Physiology Review, 75*(1), 191-236.

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventative Medicine, 10*(2), 77-84.

Araujo, A. B., Durante, R., Feldman, H. A., Goldstein, I., & McKinlay, J. B. (1998). The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosomatic Medicine, 60*(4), 458-465.

Beekman, A. T., Deeg, D. J., Van Limbeek, J., Braam, A. W., De Vries, M. Z., & Van Tilburg, W. (1997). Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychological Medicine, 27*(1), 231-235.

Beekman, A. T., Penninx, B. W., Deeg, D. J., Ormel, J., Braam, A. W., & van Tilburg, W. (1997). Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). *Journal of Affective Disorders, 46*(3), 219-231.

Benet, A. E., & Melman, A. (1995). The epidemiology of erectile dysfunction. *Urology Clinics of North America, 22*(4), 699-709.

Bennett, D. S., Ambrosini, P. J., Bianchi, M., Barnett, D., Metz, C., & Rabinovich, H. (1997). Relationship of Beck Depression Inventory factors to depression among adolescents. *Journal of Affective Disorders, 45*(3), 127-134.

Berkman, L. F., Berkman, C. S., Kasl, S., Freeman, D. H., Jr., Leo, L., Ostfeld, A. M., Cornoni-Huntley, J., & Brody, J. A. (1986). Depressive symptoms in relation to physical health and functioning in the elderly. *American Journal of Epidemiology, 124*(3), 372-388.

Bonin-Guillaume, S., Clement, J. P., Chassain, A. P., & Leger, J. M. (1995). [Psychometric evaluation of depression in the elderly subject: which instruments? What are the future perspectives?]. *Encephale, 21*(1), 25-34.

Boolell, M., Allen, M. J., Ballard, S. A., Gepi-Attee, S., Muirhead, G. J., Naylor, A. M., Osterloh, I. H., & Gingell, C. (1996). Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *International Journal of Impotence Research, 8*(2), 47-52.

Buffum, J. (1986). Pharmacosexology update: prescription drugs and sexual function. *Journal of Psychoactive Drugs, 18*(2), 97-106.

Burchardt, M., Burchardt, T., Anastasiadis, A. G., Kiss, A. J., Shabsigh, A., de La Taille, A., Pawar, R. V., Baer, L., & Shabsigh, R. (2001). Erectile dysfunction is a marker for cardiovascular complications and psychological functioning in men with hypertension. *International Journal of Impotence Research, 13*(5), 276-281.

Cheitlin, M. D., Hutter, A. M., Jr., Brindis, R. G., Ganz, P., Kaul, S., Russell, R. O., Jr., & Zusman, R. M. (1999). ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/American Heart Association. *Journal of the American College of Cardiology, 33*(1), 273-282.

Cheng, T. O. (1999). Definition of heart failure. *European Journal of Heart Failure, 1*(4), 433-434.

Chibnall, J. T., & Tait, R. C. (1994). The short form of the Beck Depression Inventory: validity issues with chronic pain patients. *Clinics of Joint Pain, 10*(4), 261-266.

Christ, G. J. (1995). The penis as a vascular organ. The importance of corporal smooth muscle tone in the control of erection. *Urology Clinics of North America, 22*(4), 727-745.

Cleland, J. G., & Wang, M. (1999). Depression and heart failure--not yet a target for therapy? *European Heart Journal, 20*(21), 1529-1531.

Cowie, M. R., Mosterd, A., Wood, D. A., Deckers, J. W., Poole-Wilson, P. A., Sutton, G. C., & Grobbee, D. E. (1997). The epidemiology of heart failure. *European Heart Journal, 18*(2), 208-225.

DeBusk, R., Drory, Y., Goldstein, I., Jackson, G., Kaul, S., Kimmel, S. E., Kostis, J. B., Kloner, R. A., Lakin, M., Meston, C. M., Mittleman, M., Muller, J. E., Padma-Nathan, H., Rosen, R. C., Stein, R. A., & Zusman, R. (2000). Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. *American Journal of Cardiology, 86*(2A), 62F-68F.

DeBusk, R. F. (2002). Sildenafil and physical exertion in men with coronary artery disease. *Journal of the American Medical Association, 287*(18), 2359; discussion 2359-2360.

Dominguez, L. J., Parrinello, G., Amato, P., & Licata, G. (1999). Trends of congestive heart failure epidemiology: contrast with clinical trial results. *Cardiologia, 44*(9), 801-808.

Drory, Y., Kravetz, S., Florian, V., & Weingarten, M. (1998). Sexual activity after first acute myocardial infarction in middle-aged men: demographic, psychological and medical predictors. *Cardiology, 90*(3), 207-211.

Duer, S., Schwenk, T. L., & Coyne, J. C. (1988). Medical and psychosocial correlates of self-reported depressive symptoms in family practice. *Journal of Family Practice, 27*(6), 609-614.

Feinstein, A. (1970). The pre-therapeutic classification of comorbidity in chronic disease. *Journal of Chronic Disease, 23*, 455.

Feldman, H. A., Goldstein, I., Hatzichristou, D. G., Krane, R. J., & McKinlay, J. B. (1994). Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *Journal of Urology, 151*(1), 54-61.

Foelker, G. A., Jr., & Shewchuk, R. M. (1992). Somatic complaints and the CES-D. *Journal of the American Geriatric Society, 40*(3), 259-262.

Freedland, K. E., Carney, R. M., Rich, M. W., Caracciolo, A., Krotenberg, J. A., Smith, L. J., & Sperry, J. (1991). Depression in elderly patients with congestive heart failure. *Journal of Geriatric Psychiatry, 24*(1), 59-71.

Friedman, M. M., & Griffin, J. A. (2001). Relationship of physical symptoms and physical functioning to depression in patients with heart failure. *Heart Lung, 30*(2), 98-104.

Friedman, S. (2000). Cardiac disease, anxiety, and sexual functioning. *American Journal of Cardiology, 86*(2A), 46F-50F.

Gerety, M. B., Williams, J. W., Jr., Mulrow, C. D., Cornell, J. E., Kadri, A. A., Rosenberg, J., Chiodo, L. K., & Long, M. (1994). Performance of case-finding tools for depression in the nursing home: influence of clinical and functional characteristics and selection of optimal threshold scores. *Journal of the American Geriatric Society, 42*(10), 1103-1109.

Giuliano, F., Montorsi, F., Mirone, V., Rossi, D., & Sweeney, M. (2000). Switching from intracavernous prostaglandin E1 injections to oral sildenafil citrate in patients with erectile dysfunction: results of a multicenter European study. The Sildenafil Multicenter Study Group. *Journal of Urology, 164*(3 Pt 1), 708-711.

Goldstein, I. (2000). The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. *American Journal of Cardiology, 86*(2A), 41F-45F.

Goldstein, I., Lue, T. F., Padma-Nathan, H., Rosen, R. C., Steers, W. D., & Wicker, P. A. (1998). Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *New England Journal of Medicine, 338*(20), 1397-1404.

Golin, S., & Hartz, M. A. (1979). A factor analysis of the Beck Depression Inventory in a mildly depressed population. *Journal of Clinical Psychology, 35*(2), 322-325.

Gutierrez, R. C. (1997). *Optimal Method of Assesing Depression in Patients with Congestive Heart Failure.*, University of Alberta, Edmonton, Alberta.

Gutierrez, R. C., & Davis, T. (1999). Assessing Depression in Patients with Congestive Heart Failure. *Canadian Journal of Cardiovascular Nursing, 10*(4), 29-36.

Harding, R., & Golombok, S. (2002). Test-retest reliability of the measurement of penile dimensions in a sample of gay men. *Archives of Sexual Behavior, 31*(4), 351-357.

Hebert, R. M., Crement, T. P., & Ferguson, R. (2000). Sildenafil in the Treatment of Erectile Dysfunction in Males with Heart Failure. American Heart Association - conference abstract: American Heart Association.

Herrmann, H. C., Chang, G., Klugherz, B. D., & Mahoney, P. D. (2000). Hemodynamic effects of sildenafil in men with severe coronary artery disease. *New England Journal of Medicine, 342*(22), 1622-1626.

Himmelfarb, S., & Murrell, S. A. (1983). Reliability and validity of five mental health scales in older persons. *Journal of Gerontology, 38*(3), 333-339.

Jaarsma, T., Dracup, K., Walden, J., & Stevenson, L. W. (1996). Sexual function in patients with advanced heart failure. *Heart Lung, 25*(4), 262-270.

Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gaulden, L. H., Cuffe, M. S., Blazing, M. A., Davenport, C., Califf, R. M., Krishnan, R. R., & O'Connor, C. M. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine, 161*(15), 1849-1856.

Johannes, C. B., Araujo, A. B., Feldman, H. A., Derby, C. A., Kleinman, K. P., & McKinlay, J. B. (2000). Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *Journal of Urology, 163*(2), 460-463.

Kannel, W. B., & Belanger, A. J. (1991). Epidemiology of heart failure. *American Heart Journal, 121*(3 Pt 1), 951-957.

Kannel, W. B., Feinleib, M., McNamara, P. M., Garrison, R. J., & Castelli, W. P. (1979). An investigation of coronary heart disease in families. The Framingham offspring study. *American Journal of Epidemiology, 110*(3), 281-290.

Kinzie, J. D., Lewinsohn, P., Maricle, R., & Teri, L. (1986). The relationship of depression to medical illness in an older community population. *Comprehensive Psychiatry, 27*(3), 241-246.

Kloner, R. A. (2000). Sex and the patient with cardiovascular risk factors: focus on sildenafil. *American Journal of Medicine, 109 Suppl 9A*, 13S-21S; discussion 29S-30S.

Langtry, H. D., & Markham, A. (1999). Sildenafil: a review of its use in erectile dysfunction. *Drugs, 57*(6), 967-989.

Leahy, J. M. (1992). Validity and reliability of the Beck Depression Inventory-Short Form in a group of adult bereaved females. *Journal of Clinical Psychology, 48*(1), 64-68.

Lecrubier, Y. (2001). The burden of depression and anxiety in general medicine. *Journal of Clinical Psychiatry, 62*(Suppl 8), 4-9; discussion 10-11.

Lyness, J. M., Noel, T. K., Cox, C., King, D. A., Conwell, Y., & Caine, E. D. (1997). Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. *Archives of Internal Medicine, 157*(4), 449-454.

Majani, G., Pierobon, A., Giardini, A., Callegari, S., Opasich, C., Cobelli, F., & Tavazzi, L. (1999). Relationship between psychological profile and cardiological variables in chronic heart failure. The role of patient subjectivity. *European Heart Journal, 20*(21), 1579-1586.

Malozowski, S., & Sahlroot, J. T. (2002). Sildenafil and physical exertion in men with coronary artery disease. *Journal of the American Medical Association, 287*(18), 2359; discussion 2359-2360.

Manecke, R. G., & Mulhall, J. P. (1999). Medical treatment of erectile dysfunction. *Annals of Medicine, 31*(6), 388-398.

Massie, B. M., & Shah, N. B. (1997). Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. *American Heart Journal, 133*(6), 703-712.

McKinlay, J. B. (1989). Is there an epidemiologic basis for a male climacteric syndrome? The Massachusetts Male Aging Study. *Progressive Clinical and Biological Research, 320*, 163-192.

Melman, A., & Gingell, J. C. (1999). The epidemiology and pathophysiology of erectile dysfunction. *Journal of Urology, 161*(1), 5-11.

Mertens, C., Merckx, L., Derluyn, M., & van den Brande, P. (1994). Iatrogenic femoral arteriovenous fistula as a cause of erectile dysfunction. *European Urology, 26*(4), 340-341.

Meuleman, E. J. (2002). Prevalence of erectile dysfunction: need for treatment? *Inernational Journal of Impotence Research, 14 Suppl 1*, S22-28.

Michelakis, E., Tymchak, W., & Archer, S. (2000). Sildenafil: from the bench to the bedside. *Canadian Medical Association Journal, 163*(9), 1171-1175.

Moller, A., Wiedemann, G., Rohde, U., Backmund, H., & Sonntag, A. (1994). Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis. *Acta Psychiatr Scand, 89*(2), 117-121.

Moller, J., Ahlbom, A., Hulting, J., Diderichsen, F., de Faire, U., Reuterwall, C., & Hallqvist, J. (2001). Sexual activity as a trigger of myocardial infarction. A case-crossover analysis in the Stockholm Heart Epidemiology Programme (SHEEP). *Heart, 86*(4), 387-390.

Morrison, H. (2000). Sildenafil (Viagra): cardiac risks. *Canadian Journal of Cardiology, 163*(1), 86-87, 90-81.

Muller, J. E. (2000). Triggering of cardiac events by sexual activity: findings from a case- crossover analysis. *American Journal of Cardiology, 86*(2A), 14F-18F.

Muller, M. J., & Benkert, O. (2001). Lower self-reported depression in patients with erectile dysfunction after treatment with sildenafil. *Journal of Affective Disorders, 66*(2-3), 255-261.

Myers-Grender, J., & Johnson, W.D. (1994). Fitting multivariate polynomial growth curves in two-period cross-over designs. *Statistics in Medicine, 13,* 931-943.

NIH Consensus Conference. (1993). NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *Journal of the American Medical Association, 270*(1), 83-90.

Olsson, A. M., & Persson, C. A. (2001). Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease. *Int J Clin Pract, 55*(3), 171-176.

Papassotiropoulos, A., & Heun, R. (1999). Screening for depression in the elderly: a study on misclassification by screening instruments and improvement of scale performance. *Progressive Neuropsychopharmacological and Biological Psychiatry, 23*(3), 431-446.

Peveler, R., Carson, A., & Rodin, G. (2002). Depression in medical patients. *British Medical Journal, 325*(7356), 149-152.

Plaud, J. J., Dubbert, P. M., Holm, J., Wittrock, D., Smith, P., Edison, J., McAnulty, R., Caddell, J., Summerville, M., & Jones, A., Jr. (1996). Erectile dysfunction in men with chronic medical illness. *Journal of Behavioral Therapy and Experimental Psychiatry, 27*(1), 11-19.

Price, D. E., Gingell, J. C., Gepi-Attee, S., Wareham, K., Yates, P., & Boolell, M. (1998). Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. *Diabet Med, 15*(10), 821-825.

Reynolds, W. M., & Gould, J. W. (1981). A psychometric investigation of the standard and short form Beck Depression Inventory. *Journal of Consulting Clinical Psychology, 49*(2), 306-307.

Roberts, R. E., Lewinsohn, P. M., & Seeley, J. R. (1991). Screening for adolescent depression: a comparison of depression scales. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(1), 58-66.

Roberts, R. E., & Vernon, S. W. (1983). The Center for Epidemiologic Studies Depression Scale: its use in a community sample. *American Journal of Psychiatry, 140*(1), 41-46.

Roose, S. P., & Seidman, S. N. (2000). Sexual activity and cardiac risk: is depression a contributing factor? *American Journal of Cardiology, 86*(2A), 38F-40F.

Rosen, R. C., Riley, A., Wagner, G., Osterloh, I. H., Kirkpatrick, J., & Mishra, A. (1997). The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology, 49*(6), 822-830.

Ruiz, A., Silva, H., & Miranda, E. (2001). [Clinical and psychometric diagnosis of depression in patients in general medicine]. *Rev Med Chil, 129*(6), 627-633.

Schotte, C. K., Maes, M., Cluydts, R., De Doncker, D., & Cosyns, P. (1997). Construct validity of the Beck Depression Inventory in a depressive population. *Journal of Affective Disorders, 46*(2), 115-125.

Scogin, F., Beutler, L., Corbishley, A., & Hamblin, D. (1988). Reliability and validity of the short form Beck Depression Inventory with older adults. *Journal of Clinical Psychology, 44*(6), 853-857.

Seidman, S. N. (2002). Exploring the relationship between depression and erectile dysfunction in aging men. *Journal of Clinical Psychiatry, 63*(Suppl 5), 5-12; discussion 23-15.

Seidman, S. N., & Roose, S. P. (2001). Sexual dysfunction and depression. *Current Psychiatric Report, 3*(3), 202-208.

Senni, M., Tribouilloy, C. M., Rodeheffer, R. J., Jacobsen, S. J., Evans, J. M., Bailey, K. R., & Redfield, M. M. (1999). Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Archives of Internal Medicine, 159*(1), 29-34.

Servoss, S. J., Januzzi, J. L., & Muller, J. E. (2002). Triggers of acute coronary syndromes. *Progress in Cardiovascular Disease, 44*(5), 369-380.

Shabsigh, R. (1999). Efficacy of sildenafil citrate (VIAGRA) is not affected by aetiology of erectile dysfunction. *International Journal of Clinical Practice: supplement, 102*, 19-20.

Shabsigh, R., Zakaria, L., Anastasiadis, A. G., & Seidman, A. S. (2001). Sexual dysfunction and depression: etiology, prevalence, and treatment. *Current Urology Reports, 2*(6), 463-467.

Simonsen, U. (2002). Interactions between drugs for erectile dysfunction and drugs for cardiovascular disease. *International Journal of Impotence Research, 14*(3), 178-188.

Singh, A. R., & Newton, W. P. (2002). Several depression screening tools work equally well. *Journal of Family Practice, 51*(6), 511.

Stein, R. A. (2000). Cardiovascular response to sexual activity. *American Journal of Cardiology, 86*(2A), 27F-29F.

Sullivan, M. J., Weinshenker, B., Mikail, S., & Bishop, S. R. (1995). Screening for major depression in the early stages of multiple sclerosis. *Canadian Journal of Neurological Sciences, 22*(3), 228-231.

Teo, K. K., Ignaszewski, A. P., Gutierrez, R., Hill, K. L., Martin, S. L., Calhoun, H. P., Humen, D. P., & Montague, T. J. (1992). Contemporary medical management of left ventricular dysfunction and congestive heart failure. *Canadian Journal of Cardiology, 8*(6), 611-619.

Thomas, J. L., Jones, G. N., Scarinci, I. C., Mehan, D. J., & Brantley, P. J. (2001). The utility of the CES-D as a depression screening measure among low- income women attending primary care clinics. The Center for Epidemiologic Studies-Depression. *International Journal of Psychiatric Medicine, 31*(1), 25-40.

U.S. Department of Health and Human Services. (1993). *Depression in Primary Care: Detection and Diagnosis. Clinical Practice Guideline 1 (No. 93-0550).* Rockville, MD: Public Health Service. Agency for Health Care Policy & Research.

Vaccarino, V., Kasl, S. V., Abramson, J., & Krumholz, H. M. (2001). Depressive symptoms and risk of functional decline and death in patients with heart failure. *Journal of the American College of Cardiology, 38*(1), 199-205.

Vardi, Y., Klein, L., Nassar, S., Sprecher, E., & Gruenwald, I. (2002). Effects of sildenafil citrate (viagra) on blood pressure in normotensive and hypertensive men. *Urology, 59*(5), 747-752.

Wagner, G., & Saenz de Tejada, I. (1998). Update on male erectile dysfunction. *British Medical Journal, 316*(7132), 678-682.

Weissman, M. M., Pottenger, M., Kleber, H., Ruben, H. L., Williams, D., & Thompson, W. D. (1977). Symptom patterns in primary and secondary depression. A comparison of primary depressives with depressed opiate addicts, alcoholics, and schizophrenics. *Archives of General Psychiatry, 34*(7), 854-862.

Weissman, M. M., Sholomskas, D., Pottenger, M., Prusoff, B. A., & Locke, B. Z. (1977). Assessing depressive symptoms in five psychiatric populations: a validation study. *American Journal of Epidemiology, 106*(3), 203-214.

Williams, S. A., Kasl, S. V., Heiat, A., Abramson, J. L., Krumholz, H. M., & Vaccarino, V. (2002). Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosomatic Medicine, 64*(1), 6-12.

Yusuf, S., Thom, T., & Abbott, R. D. (1989). Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension, 13*(5 Suppl), I74-79.

Zich, J. M., Attkisson, C. C., & Greenfield, T. K. (1990). Screening for depression in primary care clinics: the CES-D and the BDI. *International Journal of Psychiatric Medicine, 20*(3), 259-277.

Appendix A

RE: permission for figure

From: l.toyne@elsevier.com
To: Webster, Linda
Cc:
Subject: RE: permission for figure
Sent: 10/1/02 9:59 AM
Importance: Normal

In response to your request to use:

Journal Name Year Citation Item

American Journal of Cardiology 2000 86(2A) p.45F

Intended Use: To use material in a thesis for Masters in Nursing Program

PERMISSION GRANTED

Rights granted herein are non-exclusive and limited to one time only reproduction in printed format in the English language. Your credit line must include the name of the publication, issue, date, volume, and page number, as well as "Copyrighted (year of publication), American Journal of Cardiology.

L.Toyne
Editorial permissions office

Linda Webster
lnwebste@cha.ab.ca
University of Alberta

Appendix B

Erectile Physiology and Treatment of Erectile Dysfunction

Erectile Physiology

Andersson and Wagner (1995) described the erectile process as being a result of nervous and vascular system mediation. Christ (1995) described it as being predominantly regulated by vascular and smooth muscle function. There is a consensus that erection is a neurovascular phenomenon.

Erection is a direct result of sexual stimulation that activates non-adrenergic, non-cholinergic nerves in the penis; hence nerve discharge. This leads to activation of neural nitric oxide synthase and to the secretion of the neurotransmitter nitric oxide, a potent vasodilator, from the nerve terminals. In turn, this results in relaxation of both the vascular structures in the corpus cavernosum and the cavernosal smooth muscle. Together, the effects permit entry of blood into distensible cavernous spaces under arterial pressure. This rapid in-flow compresses venous drainage vessels against the non-accommodating tunica albuginea, resulting in engorgement of the body of the penis and rigid erection (Michelakis et al., 2000).

In order to initiate and sustain erection, a continuous supply of cyclic guanomonophosphate (cGMP) is required. cGMP levels depend on the balance between formation and continuous degradation by phosphodiesterases (PDE) (particularly PDE 5). Thus, inhibition of PDE 5 by medications such as sildenafil enhances cGMP levels thereby promoting erection (Michelakis et al., 2000). Figure 11 illustrates this process.

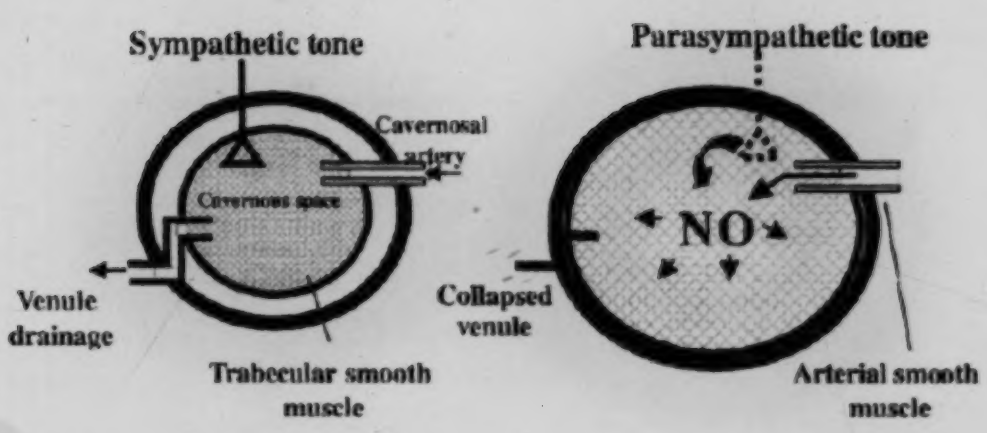


Figure 11. The mechanism of erection and the role of nitric oxide (Michelakis et al., 2000)[8] (see Appendix L).

[8]From "Sildenafil: from the bench to the bedside," by E. Michelakis et al., 2000, *Canadian Medical Association Journal, 9,* p. 1173. Copyright 2000 by the Canadian Medical Association Journal. Adapted with permission of the author.

Appendix C

The Treatment of Erectile Dysfunction

Intracavernosal injections of prostaglandin E_1, penile implants, vascular surgery, or vacuum constriction devices were limited medical solutions in the quest for return to normal sexual functioning for this population (Giuliano, Montorsi, Mirone, Rossi, & Sweeney, 2000; Goldstein et al., 1998). These alternatives were successful in up to 79% of erectile dysfunction patients, but involved invasive procedures, surgical techniques and/or devices (Giuliano et al., 2000). They did not foster the spontaneity that is desirable for intercourse.

Sildenafil. Sildenafil (Viagra®) became available to the general public in 1998 as a treatment for ED after originally being studied as an agent for the treatment of hypertension. Early trial investigators became alerted to "side-effects" when study medication was not being returned. Extensive investigation by Pfizer revealed that the research subjects had discovered the erectile properties of sildenafil. This effect occurs rapidly, usually within one hour of ingestion, and is relatively short-lived (4 hours) (Langtry & Markham, 1999). Sildenafil improves frequency, hardness, and duration of erections, as well as ability to achieve and maintain erections adequate for sexual intercourse. It is effective in improving erectile dysfunction of most etiology (ie., diabetes, hypertension, spinal cord injury (Langtry & Markham, 1999).

Sildenafil inhibits PDE 5 thus limiting the breakdown of cGMP. The elevated levels of cGMP allow penile vasodilatation necessary for functional erection (see Figure 12).

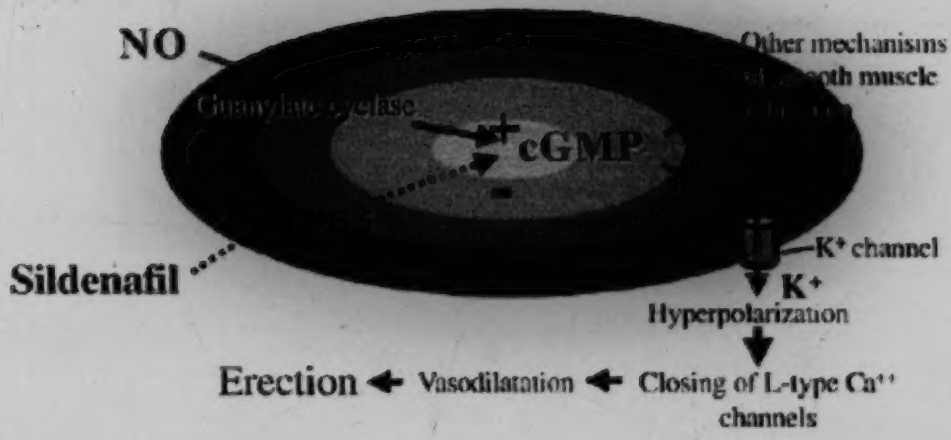


Figure 12. "The intracellular activities within a single smooth muscle cell and the effect of sildenafil on erection. In this schematic, plus symbols and solid arrows indicate activation, and minus symbols and broken arrows indicate inhibition" (Michelakis et al., 2000)[9] (see Appendix L).

[9]From "Sildenafil: from the bench to the bedside," by E. Michelakis et al., 2000, Canadian Medical Association Journal, 9, p. 1173. Copyright 2000 by the Canadian Medical Association Journal. Adapted with permission of the author.

Sildenafil only exerts this desired effect after sexual stimulation induces an initial release of nitric oxide. The erectile effect does not occur spontaneously upon the ingestion of the medication and thus priapism is not a problem

Pharmacology of sildenafil. Sildenafil is metabolized in the liver and excreted in the feces and urine. Caution must be exercised in patients with liver disease, though liver dysfunction is not an absolute contraindication because the drug is only used intermittently.

The adverse effect profile includes common vasodilation side effects (transient headache (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), and abnormal vision (3%) related to inhibition of PDE 3) (Langtry & Markham, 1999). Side effects are a direct result of PDE 5, though chiefly expressed in the penis, is mildly active in other tissues such as the retina and gastrointestinal tract. The usual dosage is 25 milligrams (mg) to 100 mg once daily (Michelakis et al., 2000). Doses of 200 mg have been used in healthy volunteers without ill effect (Boolell et al., 1996).

Appendix D

Sildenafil and Congestive Heart Failure

Sildenafil (Viagra) has shown an 84% efficacy rate in treatment of erectile dysfunction (Feldman et al., 1994). To date, it has been presumed that congestive heart failure and the use of sildenafil is relatively contraindicated (Cheitlin et al., 1999) based largely on exclusion of these patients from clinical trials. This has been the result of an unfounded concern that sildenafil potentiates vasodilatory effects of current therapies thus possibly resulting in a hypotensive crisis. Conventional pharmacological intervention in congestive heart failure aims to decrease arterial blood pressure in an effort to decrease systemic vascular resistance. This makes the use of medications that can treat erectile dysfunction by promoting vasodilatation, such as sildenafil, potentially problematic in these patients. Although previous clinical trials have not prospectively assessed this drug-drug interaction, retrospective analysis does not indicate an increase in adverse hypotensive effects resulting from the combination of these medications (Cheitlin et al., 1999). Because sildenafil is a weak vasodilator (mean arterial pressure decreases 5.3 mmHG (Vardi, Klein, Nassar, Sprecher, & Gruenwald, 2002), its use in congestive heart failure may not be problematic. In addition, recent studies show that sildenafil neither impairs coronary flow reserve (Herrmann, Chang, Klugherz, & Mahoney, 2000) nor compromises exercise performance in males with known coronary artery disease (Malozowski & Sahlroot, 2002). Unless men with congestive heart failure are receiving nitrate therapy, this assumption may be unfounded provided prudent measures for safety are assessed prior to commencing treatment (Michelakis et al., 2000). Sildenafil is contraindicated in those taking nitrates as they may amplify the hypotensive effects of the

nitrates. Nitrates stimulate the nitric oxide/cGMP pathway, thus increasing circulating cGMP. Since sildenafil's desired action is to prevent the breakdown of cGMP, excessive levels may lead to prolonged and excessive hypertension that could potentially cause bodily harm and even death (Simonsen, 2002). Such interaction has not been found with any other medications (Simonsen, 2002).

Previous clinical trials studying the efficacy of sildenafil on those with cardiac disease have been centered on populations with coronary artery disease and recent myocardial infarctions (Cheitlin et al., 1999; DeBusk et al., 2000; Herrmann et al., 2000; Johannes et al., 2000; Morrison, 2000; Muller, 2000). These trials used the IIEF, a fifteen item questionnaire that assesses efficacy of erectile function, sexual desire, and satisfaction with intercourse (Rosen et al., 1997). This questionnaire consistently determined functional success of treatment with sildenafil and all studies indicated statistically significant (p-values 0.01-0.0001) improvement in pre to post questionnaire scores.

Hebert, Crement, and Ferguson (2000) presented a small, unpublished, trial in a poster abstract at the American Heart Association annual meeting in New Orleans, Louisiana, November 2000. This study described 32 congestive heart failure clients (unspecified NYHA classification) during a 30 day trial with open-label sildenafil for the treatment of erectile dysfunction. It suggested favorable functional results, but did not address areas of sexual satisfaction, emotional or depressive issues related to erectile dysfunction in this population.

The Safety of Intercourse and Congestive Heart Failure

There is concern about the safety of intercourse in patients with congestive heart failure (ie., it may precipitate a myocardial infarction leading to death). Both patients and medical staff feel this concern. There is basis for this concern as studies have shown an increased incidence of myocardial infarction during periods of intercourse and shortly thereafter (DeBusk et al., 2000; DeBusk, 2002; Moller et al., 2001; Servoss, Januzzi, & Muller, 2002). Muller (2000) stated that sexual dysfunction in the cardiac patient was psychological in nature stemming from fear on the part of both partners that sexual activity may trigger a lethal coronary event. He cited that 70% reported such concerns though only 39% decreased the frequency of sexual activity in practice (Muller, 2000).

DeBusk et al. (2000) described necessary metabolic energy requirements for various levels of sexual performance as 2-3 metabolic equivalents of oxygen consumption (METS) required for the pre-orgasmic phase and 3-4 METS during the orgasmic phase. These measures were rudimentary guidelines and were to be as individual as the people to which they would apply. Variation for sexual positions and length of time sexual activity takes place must be taken into account. Cheitlin et al., (1999) indicated that the ability of patients to achieve 5-6 METS in a modified Bruce exercise tolerance test would probably be clinically indicative of low risk potential for developing myocardial ischemia during intercourse. Patient education and encouragement of continued of sexual expression should be addressed with clients experiencing symptoms of heart disease (Andersson & Stief, 2000; DeBusk et al., 2000; Muller, 2000; Stein, 2000).

Appendix E

<<DATE>>

<<NAME>>
<<ADDRESS>>
<<CITY>>, Alberta
<<POSTAL CODE>>

RE: Clinical Trial Participation

Dear Mr. <<NAME>>,

A physician-led study has recently been started in the University of Alberta Hospitals - Heart Function Clinic to study the use of Viagra in erectile dysfunction. All male clinic patients, except those on certain medications, are potentially eligible and so this letter has been sent all patients, despite the fact many may not suffer from erectile dysfunction. ***If you do not have erectile dysfunction or are for any reason not interested in participating please disregard this letter.*** As always, information in your patient record remains strictly confidential without your permission for the study investigators to access your clinic record.

This trial is investigating a treatment for impaired sexual function (erectile dysfunction) in men with heart failure. A study of North American males determined that erectile dysfunction commonly occurs in men as they age (40 year olds – 39%, 70 year olds – 67%). Heart failure patients experience erectile dysfunction even more frequently than the general population, since impaired circulation hinders adequate blood flow necessary for satisfactory erections. In addition, medications used in the treatment of heart failure may worsen erectile function.

Viagra is a pill that is available for the treatment of erectile dysfunction. It is safe and effective in the general population with erectile dysfunction. It is not known whether Viagra is as effective or as safe in heart failure patients as in those without heart failure.

This is a twelve-week study in which Viagra will be assessed for its possible erectile benefits in heart failure patients. This trial will examine its use in a controlled environment under the supervision of heart failure specialists. Viagra may become a more favorable treatment option for men with heart failure if the results of this study are favorable.

We are currently looking for patients from the heart function clinic with the following characteristics:

1. A diagnosis of heart failure on medication (i.e., lasix, beta-blockers, ace-inhibitors).
2. Erectile dysfunction (difficulty either attaining or maintaining an erection necessary for satisfactory sexual performance).
3. Absence of chest pain or nitroglycerine use.

Should you wish to discuss the details of this trial, please call the study investigator/coordinator:

Sincerely,

Dr. Stephen Archer
Principal Investigator-Division of Cardiology

Linda Webster R.N, BScN.
Coordinator/Investigator 407-3285

Appendix F

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Patient Initials _____ _____ _____ Patient Study Number _____

Visit #_____ Date:_____

OVER THE PAST FOUR WEEKS

Q1.	How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time 5 = Almost always / always
Q2.	When you had erections with sexual stimulation how often were your erections hard enough for penetration?	
Q3.	When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never / never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time 5 = Almost always / always
Q4.	During sexual intercourse, *how often* were you able to maintain your erection after you had penetrated (entered) your partner?	
Q5.	During sexual intercourse, *how difficult* was it to maintain your erection to completion of intercourse?	1 = Did not attempt intercourse 2 = Very difficult 3 = Extremely difficult 4 = Slightly difficult 5 = Not difficult
Q6.	How many times have you attempted sexual intercourse?	0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven + attempts

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Patient Initials _____ _____ _____ Patient Study Number _____

Visit #_____ Date:_____

OVER THE PAST 4 WEEKS

Q7.	When you attempted sexual intercourse, how often was it satisfactory for you?	0 = Did not attempt intercourse 1 = Almost never / never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always / always
Q8.	How much have you enjoyed sexual intercourse?	0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highly enjoyable 5 = Very highly enjoyable
Q9.	When you had sexual stimulation *or* intercourse how often did you ejaculate?	0 = No sexual stimulation/ intercourse 1 = Almost never / never 2 = A few times (much less than half the time 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always / always
Q10.	When you had sexual stimulation *or* intercourse how often did you have the feeling of orgasm or climax?	
Q11.	How often have you felt sexual desire?	1 = Almost never / never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always / always
Q12.	How would you rate your level of sexual desire?	1 = Very low / none at all 2 = Low 3 = Moderate 4 = High 5 = Very high

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Patient Initials _____ _____ _____ Patient Study Number _____

Visit #_____ Date:_____

OVER THE PAST 4 WEEKS

Q13.	How satisfied have you been with your overall *sex life*?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied And dissatisfied 4 = Moderately satisfied 5 = Very satisfied
Q14.	How satisfied have you been with your *sexual relationship* with your partner?	
Q15.	How do you rate your *confidence* that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

Appendix G

The Center for Epidemiologic Studies – Depression Scale

DURING THE PAST WEEK:

	Rarely or none of the time (Less than 1 day)	Some or little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
I was bothered by things that usually don't bother me				
I did not feel like eating; my appetite was poor				
I felt that I could not shake off the blues even with help from my family and friends				
I felt that I was just as good as other people				
I had trouble keeping my mind on what I was doing				
I felt depressed				
I felt that everything I did was an effort				
I felt hopeful about the future				
I thought my life had been a failure				
I felt fearful				
My sleep was restless				
I was happy				
I talked less than usual				
I felt lonely				
People were unfriendly				
I enjoyed life				
I had crying spells				
I felt sad				
I felt that people disliked me				
I could not get "going"				

Appendix H

Health Research Ethics Board biomedical research health research

2J2.27 Walter Mackenzie Centre
University of Alberta. Edmonton. Alberta T6G 2R7
p.780.492.9724 f.780.492.7303
ethics@med.ualberta.ca

3-48 Corbett Hall. University of Alberta
Edmonton. Alberta T6G 2G4
p.780.492.0839 f.780.492.1626
ethics@www.rehabmed.ualberta.ca

ETHICS APPROVAL FORM

Date: January 2001

Name(s) of Principal Investigator(s): Dr. Stephen Archer

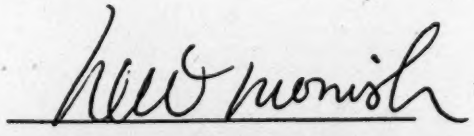
Department: Medicine

Title: The efficacy and safety of Sildenafil (Viagra) as treatment of erectile dysfunction in males with chronic heart failure (NYHA Function Class II-III)

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information material and consent form.

Specific Comments:

Signed - Chairman of Health Research Ethics Board (Biomedical)



This approval is valid for one year

Appendix I

Health Research Ethics Board biomedical research health research

2J2.27 Walter Mackenzie Centre
University of Alberta, Edmonton, Alberta T6G 2R7
p.780.492.9724 f.780.492.7303
ethics@med.ualberta.ca

3-48 Corbett Hall, University of Alberta
Edmonton, Alberta T6G 2G4
p.780.492.0839 f.780.492.1626
ethics@www.rehabmed.ualberta.ca

March 16, 2001

Dr. Stephen Archer
Division of Cardiology
2C2 WMC

RE: The efficacy and safety of Sildenafil (Viagra) as treatment of erectile dysfunction in males with chronic heart failure (NYHA Class II – III)

Dear Dr. Archer,

The Health Research Ethics Board (Biomedical Panel) has reviewed addendum 1 to the above protocol and has approved it forth with.

Specific Comments:

Signed - Chairman of Health Research Ethics Board (Biomedical)

This approval is valid for one year

Appendix J

The Efficacy and Safety of Sildenafil (Viagra®) in the Treatment Of Erectile Dysfunction in Males with Chronic Heart Failure (NYHA Functional Class II – III)

Amendment 1

March 10, 2001

Section 6.3.3 Safety Measurements

Previously read:

Ambulatory blood pressure monitoring – less than 10 mm Hg decrease in systolic measurements within four hours post trial dose of sildenafil in a clinic setting.

Changed to:

Ambulatory blood pressure monitoring for one hour prior to, and four hours post a single dose of sildenafil (50mg.) in a clinic setting. A post dose fall of > 20% of systolic baseline measurement or <80mmHg (seated, at rest) sustained for more than 30 minutes or associated with symptoms (dizziness, angina, diaphoresis) will make the subject ineligible for randomization into the trial. Potential candidates will be instructed to ingest a snack 1 –2 hours prior to the test dose of sildenafil to limit the mild vasodilatory/orthostatic hypotensive effects of the medication. Compliance with this direction in the home setting prior to ingestion of sildenafil will also be encouraged.

Section 7.3 Exclusion Criteria

Previously read:

7. History of alcohol/ substance abuse

Changed to:

7. Recent history of alcohol/substance abuse

Section 7.5 Screening Procedures

Previously read:

1). A modified Bruce stress protocol in which at least 5 METS exercise must be achieved. Ischemic EKG changes ($\geq$ 1mm of flat ST segment depression or $\geq$ 1.5 mm of upsloping ST depression) evidenced on the rest or exercise EKG will exclude the patient from the trial.

Changed to:

1). A modified Bruce stress protocol in which at least 5 METS exercise must be achieved. Ischemic EKG changes ($\geq$ 1mm of flat

ST segment depression or ≥ 1.5 mm of upsloping ST depression) evidenced on the rest or exercise EKG will exclude the patient from the trial.

Potential candidates currently receiving digoxin therapy will be asked to temporarily interrupt therapy for 1 week prior to the baseline stress test limiting the potential for false positive indications of ischemia.

Potential candidates diagnosed with left ventricular hypertrophy and/or left bundle branch blocks evidenced on the rest EKG and/or exemplifying a positive baseline stress test will have further evaluation using nuclear imaging to confirm or dismiss indicators of ischemia.

Previously read:

2). Ambulatory blood pressure monitoring for one hour prior to, and four hours post a single dose of sildenafil (50mg.) in a clinic setting. A post dose fall of > 10mmHg in systolic blood pressure (seated, at rest) sustained for more than 30 minutes or associated with symptoms (dizziness, angina, diaphoresis) will make the subject ineligible for randomization into the trail.

Changed to:

2). Ambulatory blood pressure monitoring for one hour prior to, and four hours post a single dose of sildenafil (50mg.) in a clinic setting. A post dose fall of > 20% of systolic baseline measurement or < 80mmHg (seated, at rest) sustained for more than 30 minutes or associated with symptoms (dizziness, angina, diaphoresis) will make the subject ineligible for randomization into the trial.

Section 7.9 – Follow up

Previously read:

Participants will be administered two accepted quality of life questionnaires, the Minnesota Living with Heart Failure (LIhFE) and the International Index of Erectile Function (IIEF).

Changed to:

Participants will be administered three accepted quality of life questionnaires, the Minnesota Living with Heart Failure (LihFE), the International Index of Erectile Function(IIEF), Becks Depression

Inventory (BDI), and the Center for Epidemiologic Studies – Depression scale (CES-D).

Appendix K

Sample Size

Sample size was calculated using the assumptions based on (Goldstein et al., 1998) in a 12-week double blind, placebo controlled trial studying 274 males with erectile dysfunction of varying etiologies. These participants mean IIEF scores at baseline and study termination were 12 and 20 respectively. Standard deviation was cited as $\pm$ 6.5 - $\pm$7.6. The investigators of the current studies were willing to accept a standard deviation between the groups of 10.0 given the markedly confounding variable of congestive heart failure (see Table 12).

The study will recruit 90 patients to have 78 analyzable patients assuming a 10-15% drop out rate. Group sample size of 39 and 39 (78) achieves 81% power to detect a difference of –10.0 between the null hypothesis and the alternative hypothesis assuming that the mean of group 2 is 20.0 with estimated group standard deviations of 10.0 and 10.0 with a significance level (alpha) .01 using a two-sided two sample t-test.

Table 12

Sample size table for means of 12 – 20 accepting a standard deviation of 10

Power	N1	N2	Alpha	Beta	Mean 1	Mean 2	S1	S2
0.80531	11	11	0.01	0.19469	12	20	5.0	5.0
0.81840	26	26	0.01	0.18160	12	20	8.0	8.0
0.81042	39	39	0.01	0.18958	12	20	10.0	10.0
0.80685	55	55	0.01	0.19315	12	20	12.0	12.0
0.80523	74	74	0.01	0.19477	12	20	14.0	14.0

Appendix L

Permission for use of Figure

In response to your request:

I hereby grant permission of the use of figures

"The mechanism of erection and the role of nitric oxide" (Michelakis et al., 2000)

AND

"The intracellular activities within a single smooth muscle cell and the effect of sildenafil on erection. In this schematic, plus symbols and solid arrows indicate activation, and minus symbols and broken arrows indicate inhibition" (Michelakis et al., 2000)

FROM:

"Sildenafil: from the bench to the bedside," by E. Michelakis et al., 2000, Canadian Medical Association Journal, 9, p. 1173. Copyright 2000 by the Canadian Medical Association Journal.

For use in in your Master of Nursing thesis:

E Michelakis

Dr. Evangelos Michelakis